PCT REQUEST

PH-1028-PCT

Original (for SUBMISSION) - printed on 17.11.2000 10:23:32 AM

0	**For receiving Office use only**	
0-1	International Application No.	
0-2	International Filing Date	PCT 17.11.00 受領印
0-3	Name of receiving Office and "PCT International Application"	
0-4	**Form - PCT/RO/101 PCT Request**	
0-4-1	Prepared using	PCT-EASY Version 2.91 (updated 10.10.2000)
0-5	**Petition** The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty	
0-6	**Receiving Office (specified by the applicant)**	Japanese Patent Office (RO/JP)
0-7	**Applicant's or agent's file reference**	PH-1028-PCT
I	**Title of invention**	METHOD AND SYSTEM FOR DISPLAYING DENDROGRAM
II	**Applicant**	
II-1	This person is:	applicant only
II-2	Applicant for	all designated States except US
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II-7	State of residence	JP
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III-1-7	State of residence	JP

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Original (for **SUBMISSION**) - printed on 17.11.2000 10:23:32 AM

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III-2-1	This person is:	applicant and inventor
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III-2-7	State of residence	JP
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III-4-7	State of residence	JP
IV-1	**Agent or common representative; or address for correspondence** The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:	agent
IV-1-1	Name (LAST, First)	HIRAKI, Yusuke
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IV-2	**Additional agent(s)**	additional agent(s) with same address as first named agent
IV-2-1	Name(s)	ISHII, Sadaji; WATANABE, Toshiaki

PCT REQUEST

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V	**Designation of States**	
V-1	Regional Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	EP: AT BE CH&LI CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR and any other State which is a Contracting State of the European Patent Convention and of the PCT
V-2	National Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	US
V-5	**Precautionary Designation Statement** In addition to the designations made under items V-1, V-2 and V-3, the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except any designation(s) of the State(s) indicated under item V-6 below. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit.	
V-6	**Exclusion(s) from precautionary designations**	NONE
VI-1	**Priority claim of earlier national application**	
VI-1-1	Filing date	14 December 1999 (14.12.1999)
VI-1-2	Number	Patent Application No. 11-354401
VI-1-3	Country	JP
VI-2	**Priority document request** The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s):	VI-1
VII-1	**International Searching Authority Chosen**	European Patent Office (EPO) (ISA/EP)

VIII	**Check list**	number of sheets	electronic file(s) attached
VIII-1	Request	5	-
VIII-2	Description	30	-
VIII-3	Claims	4	-
VIII-4	Abstract	1	abst1028.txt
VIII-5	Drawings	18	-
VIII-7	TOTAL	58	

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Original (for **SUBMISSION**) - printed on 17.11.2000 10:23:32 AM

	Accompanying items	paper document(s) attached	electronic file(s) attached
VIII-8	Fee calculation sheet	✓	-
VIII-9	Separate signed power of attorney	✓	-
VIII-16	PCT-EASY diskette	-	diskette
VIII-17	Other (specified):	Revenue stamps of transmittal fee for receiving office	-
VIII-17	Other (specified):	Submission of certificate of payment for search fee	-
VIII-17	Other (specified):	Submission of certificate of payment for international fee	-
VIII-18	**Figure of the drawings which should accompany the abstract**	5	
VIII-19	**Language of filing of the international application**	English	
IX-1	**Signature of applicant or agent**	Yusuke Hiraki	
IX-1-1	Name (LAST, First)	HIRAKI, Yusuke	
IX-2	**Signature of applicant or agent**	Sadaji Ishii	
IX-2-1	Name (LAST, First)	ISHII, Sadaji	
IX-3	**Signature of applicant or agent**	Toshiaki Watanabe	
IX-3-1	Name (LAST, First)	WATANABE, Toshiaki	

FOR RECEIVING OFFICE USE ONLY

10-1	**Date of actual receipt of the purported international application**	
10-2	**Drawings:**	
10-2-1	Received	
10-2-2	Not received	
10-3	**Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application**	
10-4	**Date of timely receipt of the required corrections under PCT Article 11(2)**	
10-5	**International Searching Authority**	ISA/EP
10-6	**Transmittal of search copy delayed until search fee is paid**	

PCT REQUEST

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Original (for **SUBMISSION**) - printed on 17.11.2000 10:23:32 AM

FOR INTERNATIONAL BUREAU USE ONLY

11-1	Date of receipt of the record copy by the International Bureau	

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

To:
HIRAKI, Yusuke
Toranomon No. 5 Mori Building
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JAPON

HIRAKI
JUL - 2, 2001
RECEIVED

Date of mailing (day/month/year) 21 June 2001 (21.06.01)	
Applicant's or agent's file reference PH-1028-PCT	**IMPORTANT NOTICE**

International application No.	**International filing date** (day/month/year)	**Priority date** (day/month/year)
PCT/JP00/08133	17 November 2000 (17.11.00)	14 December 1999 (14.12.99)

Applicant
HITACHI SOFTWARE ENGINEERING CO., LTD. et al

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:
   US

   In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:
   EP

   The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on
   21 June 2001 (21.06.01) under No. WO 01/45026

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, **a demand for international preliminary examination** must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the **national phase**, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44) 9/890929

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
PH-1028-PCT		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/JP 00/ 08133	17/11/2000	14/12/1999

Applicant

HITACHI SOFTWARE ENGINEERING CO., LTD. et al.

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

[ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

[ ] contained in the international application in written form.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readble form.

[ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

[X] the text is approved as submitted by the applicant.

[ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

[X] the text is approved as submitted by the applicant.

[ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. 5

[X] as suggested by the applicant.

[ ] because the applicant failed to suggest a figure.

[ ] because this figure better characterizes the invention.

[ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/JP 00/08133

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 G06F19/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 G06F G06T

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, IBM-TDB

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 99 09218 A (BERNO ANTHONY ;AFFYMETRIX INC (US)) 25 February 1999 (1999-02-25) abstract; claims 1-7 ---	1-13
Y	US 5 895 474 A (VORTMAN PNINA ET AL) 20 April 1999 (1999-04-20) the whole document ---	1-13

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 October 2001	31/10/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Filloy García, E

2

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	W LUDWIG AND O STRUNK: "ARB: A Software Environment for Sequence Data" THE MANUAL, 'Online! 16 April 1997 (1997-04-16), pages 1-43, XP002180560 München Retrieved from the Internet: <URL:http://www2.mikro.biologie.tu-muenchen.de/arb/documentation.html> 'retrieved on 2001-10-17! chapter 3, section 3 page 28 -page 29 ---	1-13
A	EISEN M B ET AL: "Cluster analysis and display of genome-wide expression patterns" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, NATIONAL ACADEMY OF SCIENCE. WASHINGTON, US, vol. 95, December 1998 (1998-12), pages 14863-14868, XP002140966 ISSN: 0027-8424 cited in the application abstract ---	1-13
A	US 5 065 347 A (PAJAK HENRY G ET AL) 12 November 1991 (1991-11-12) abstract -----	1-13

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/JP 00/08133

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9909218 A	25-02-1999	AU 9198298 A	08-03-1999
		EP 1019536 A1	19-07-2000
		WO 9909218 A1	25-02-1999
		US 6223127 B1	24-04-2001
US 5895474 A	20-04-1999	NONE	
US 5065347 A	12-11-1991	NONE	

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
21 June 2001 (21.06.2001)

PCT

(10) International Publication Number
WO 01/45026 A2

(51) International Patent Classification[7]: G06F 19/00

(21) International Application Number: PCT/JP00/08133

(22) International Filing Date:
17 November 2000 (17.11.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
11/354401 14 December 1999 (14.12.1999) JP

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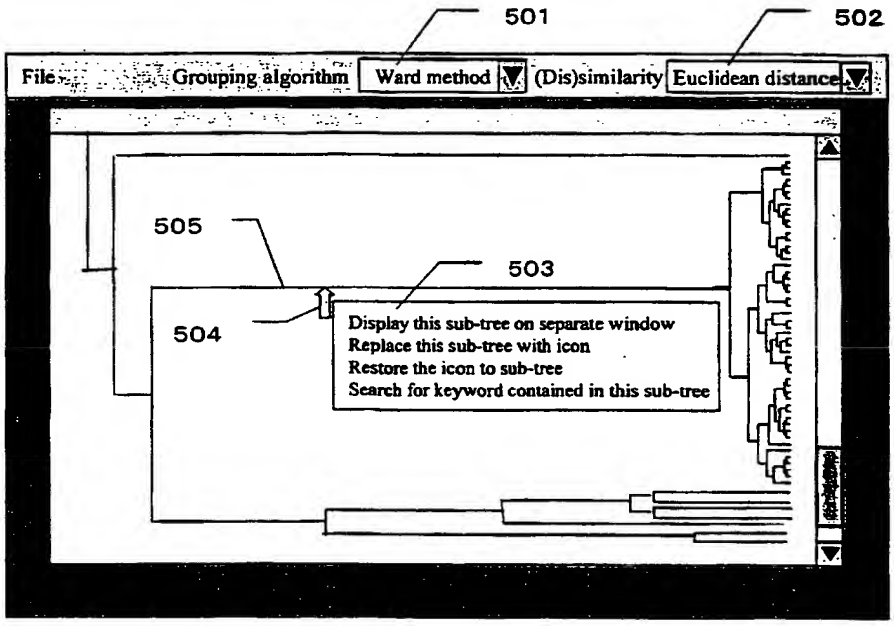
(81) Designated State *(national)*: US.

(84) Designated States *(regional)*: European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR).

Published:
— *Without international search report and to be republished upon receipt of that report.*

[Continued on next page]

(54) Title: METHOD AND SYSTEM FOR DISPLAYING DENDROGRAM



(57) Abstract: The present invention represents a global state of branches in a whole dendrogram as well as detail of states of individual subtrees, to aid focusing of groupings and selection of a clustering method. The present invention has functions of selecting a branch in a dendrogram, displaying a subtree including the selected branch and its leaves on a separate window, replacing the subtree with an icon, restoring the icon into the original subtree, and collecting and displaying keywords contained in the subtree.

WO 01/45026 A2

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

METHOD AND SYSTEM FOR DISPLAYING DENDROGRAM

FIELD OF THE INVENTION

The present invention relates to a method and a system for displaying data (gene expression data) obtained by hybridization with a specific biopolymer such as a gene, in a visually comprehensible format so that functions and roles of the biopolymer (gene) can readily be studied.

BACKGROUND OF THE INVENTION

With the increase in the number of species that have been determined of their genome sequences, so called genome comparison has extensively been performed. Genome comparison aims at finding facts based on gene differences among species, for example, finding genes involved in evolution, finding a collection of genes which are considered to be common to all species, or, conversely, studying the nature unique to specific species. The recent development of infrastructures such as DNA chips and DNA microarrays has changed the interest in the art of molecular biology from information of interspecies to information of intraspecies, namely coexpression analysis, and broadened the study covering from extraction of information to correlation of information, including the conventional comparison between species.

For example, if an unknown gene has an expression pattern identical to that of a known gene, the unknown gene

can be assumed to have a similar function to that of the known gene. Functional meanings of such genes and proteins are studied as function units or function groups. The interactions between the function units or function groups are also analyzed by correlating with known enzymatic reaction data or metabolism data, or more directly, by knocking out or overreacting a specific gene to eliminate or accelerate expression of the gene in order to study the direct and indirect influences on gene expression patterns of a whole collection of genes.

One successful case in this field would be the expression analysis of yeast by the group of P. Brown et al. from the Stanford University (Michel B. Eisen et al., Clustering analysis and display of genome-wide expression patterns, *Proc. Natl. Acad. Sci.* (1998), Dec 8; 95(25): 14863-8). They conducted hybridization of genes extracted from a cell in a time series using a DNA microarray, and numerated the expression levels thereof (i.e., numerated the brightness of the hybridized fluorescent signals). Based on the numerated values, genes having similar expression patterns in their gene cycles (genes having closer expression levels at some point) are clustered together.

Figure 1 is a diagram showing an exemplary display for showing similarity between expression patterns of genes according to the above-mentioned system. Information of each of the observed genes is listed on the right hand side, and a

dendrogram formed based on the expression patterns of these genes is drawn on the left hand side. The dendrogram is drawn by stepwisely joining every two most similar clusters together. The length of each branch corresponds to the distance (dissimilarity) between the two joined clusters. This displaying method allows a supposition that genes belonging to the same cluster may possibly share common functional characteristics.

In an actual analysis of gene expression patterns, enormous amount of data will be subjected to clustering. A DNA chip or DNA microarray is usually capable of detecting thousands to ten-thousands of genes at the same time. Generally, an expression of one gene may induce or inhibit an expression of another gene, forming a complicated network among genes. Therefore, if the numbers of genes to be observed are larger, more complicated and detailed gene network can be studied.

However, as the number of genes is increased, it becomes very difficult to find the functions of the entire genes. Since a dendrogram will represent several thousands to ten-thousands of genes, it is difficult from the display to judge what kind of grouping has been made. Furthermore, the lengths of branches in the resulting dendrogram generally differ depending on the type of clustering method employed. For example, when a furthest neighbor method is employed as a cluster combining algorithm, the average length of the

branches will be longer than the average length of branches resulting from a nearest neighbor method. Therefore, looking at overall dendrograms in Figure 2, a length from a root to leaves also varies depending on the clustering method. For clustering gene expression data, it is more important to find out the groupings than to observe the lengths of the branches. Accordingly, as shown in Figure 3, a dendrogram is generally displayed while a length from the root to the leaves of the dendrogram is fixed in advance. As a result, lengths of the branches are determined relative to the length of the whole dendrogram and a scale of the lengths of the branches differs depending on the clustering method.

According to the above-described method for displaying a dendrogram, when the dendrogram contains numbers of genes having similar expression patterns, the lengths of the branches will be short. When the lengths of these branches are too short relative to the length of the dendrogram, it becomes very difficult to find detailed relationship between the branches of genes as can be appreciated from a range **401** in Figure **4**. According to a conventional clustering for a gene expression analysis, an interactive operation such as selecting a subtree and then subjecting the selected subtree to another clustering method, was impossible. Moreover, according to a conventional clustering for a gene expression analysis, whether the grouping was successful or not is confirmed by focusing on the functions of genes or keywords

derived from gene names to see whether relative genes are assembled in a subtree. However, when the number of genes to be analyzed is numerous, it is difficult to determine which function or keyword should be focused on.

The present invention aims at solving such conventional problems, and has an objective to provide a method and a system for displaying a dendrogram such that the state of branches of the whole dendrogram can globally be understood, and such that a detailed state of each subtree can be studied.

SUMMARY OF THE INVENTION

In order to achieve the above-mentioned objective, the present invention proposes a system for displaying a dendrogram which is provided with functions for selecting a branch in a dendrogram, displaying a subtree extending from the selected branch to the downstream leaves on a separate display window, replacing the subtree with an icon, restoring the icon to the subtree, and collecting and displaying keywords contained in the subtree. According to the present invention, subtrees of a produced dendrogram can be subjected to different clustering methods interactively. Keywords contained in the subtrees can be displayed in order to confirm success of clustering as well as to aid focusing of groupings and to aid selection of a clustering method.

Hereinafter, exemplary dendrogram displays according to a dendrogram displaying system of the invention will be

described. Herein, for clearer understanding, the invention is applied to a case of genes, although the application of the present invention is not limited to genes. The present invention can equally be applied to other biopolymers such as cDNAs, RNAs, DNA fragments or the like.

Figure 5 is a view showing an exemplary display of a dendrogram resulting from a dendrogram displaying system of the invention. The display includes a grouping algorithm selection menu 501 and a (dis)similarity selection menu 502. A dendrogram is produced by reading out gene expression data, and selecting a grouping algorithm and a type of (dis)similarity. The present system may also be capable of displaying gene information next to the leaves of the dendrogram as shown in Figure 1.

By selecting a branch in the produced dendrogram, a subtree extending from the selected branch to the downstream leaves can be made the subject of operations. Specifically, the subtree can be displayed on a separate window; the subtree can be replaced with an icon; the icon can be restored to the subtree; and keywords contained in the subtree can be searched. These operations can be selected from the menu. In the figure, a branch 505 in the middle of the screen is selected with a mouse cursor 504 or the like represented by an arrow, upon which a menu window 503 appears on which selectable operations are displayed. By transferring the mouse cursor 504 to a desired operation in

the menu window 503, the selected operation is carried out.

Although Ward method is selected as a grouping algorithm in Figure 5, the selection menu 501 can be pulled down to select other algorithm such as nearest neighbor method, furthest neighbor method, group average method, centroid method, median method, flexible method or the like. Similarity or dissimilarity is an index for indicating a degree of similarity between two expression patterns. Such index may be a distance where a shorter distance represents higher similarity, or a value such as a correlation coefficient where a higher value represents higher similarity. The former index is referred to as dissimilarity and the latter as similarity. Although Euclidean distance is selected as dissimilarity in Figure 5, the selection menu 502 can be pulled down to select other types of (dis)similarity such as standardized squared Euclidean distance, Mahalanobis' general distance, Minkowsky distance or the like. The combination of grouping algorithm and dissimilarity type must be appropriate. For example, when centroid method, median method or flexible method is selected as the grouping algorithm, only squared Euclidean distance can be selected as dissimilarity.

Figure 6 is a view showing an exemplary screen displayed upon selecting a command "display this subtree on a separate window" from the menu shown in Figure 5. The selected subtree is rescaled and redisplayed according to the

length from the root to the leaves. This display technique will allow the user to find more detailed state of the branches of the subtree. According to the present system, the selected subtree can be subjected to clustering again by selecting a grouping algorithm and/or (dis)similarity. For example, clusters distant from each other (such as clusters 401 and 402, and clusters 401 and 403 in Figure 4) resulting from the first clustering can be selected and excluded to see a subtree of interest in more detail. A grouping algorithm and/or (dis)similarity can be selected from the grouping algorithm selection menu 501 and the (dis)similarity selection menu 502.

Figure 7 is a view showing an exemplary screen displayed upon selecting a command "replace this subtree with icon" from the menu shown in Figure 5. The subtree 505 can be replaced with an icon 701, by which a global state of the dendrogram can readily be observed. For example, gene groups with similar functions or gene groups with little expression observed can be assembled as a single icon.

Figure 8 is a view showing an exemplary screen displayed upon selecting a command "search for keyword contained in this subtree" from the menu shown in Figure 5. Among genes contained in the selected subtree, genes having gene information with a predetermined keywords are counted and the results are displayed as search results 801. When a keyword 802 is selected from the search results 801 with a

mouse cursor 804 or the like, genes with this keyword 802 (in the figure, "ribosomal") are marked on the dendrogram with marks 803 or the like. By doing so, types of genes assembled in the subtree can readily be known. When the grouping is found to be failed, another grouping algorithm or (dis)similarity can be selected for another clustering. This would aid selection of more appropriate clustering method.

According to the present invention, an analysis can be made effectively on a produced dendrogram.

Thus, a method for displaying a dendrogram according to the present invention comprises the steps of: clustering a plurality of types of biopolymers based on a set of data obtained by experiments of the plurality of biopolymers under different conditions, and displaying the results thereof in a dendrogram format; selecting a subtree in the dendrogram; and displaying the selected subtree on a separate window.

The present invention may comprise the steps of: designating a different clustering method for the biopolymers included in the subtree displayed on the separate window; and clustering the biopolymers included in the subtree again according to the designated clustering method, and displaying the results thereof in a dendrogram format.

Furthermore, a method for displaying a dendrogram according to the present invention comprises the steps of: clustering a plurality of types of biopolymers based on a set of data obtained by experiments of the plurality of

biopolymers under different conditions, and displaying the results thereof in a dendrogram format; selecting a subtree in the dendrogram; and replacing the selected subtree with an icon.

If necessary, the method may further comprise a step of restoring the subtree icon to the original dendrogram subtree format.

A method for displaying a dendrogram according to the present invention comprises the steps of: clustering a plurality of types of biopolymers based on a set of data obtained by experiments of the plurality of biopolymers under different conditions, and displaying the results thereof in a dendrogram format; selecting a subtree in the dendrogram; and from the biopolymers included in the selected subtree, counting and displaying the number of biopolymers containing in their biopolymer information a keyword from a keyword dictionary file.

A method for displaying a dendrogram according to the present invention comprises the steps of: clustering a plurality of types of biopolymers based on a set of data obtained by experiments of the plurality of biopolymers under different conditions, and displaying the results thereof in a dendrogram format; selecting a subtree in the dendrogram; designating a keyword; and displaying a location of a biopolymer in the dendrogram, which includes the designated keyword in its biopolymer information.

According to the above-described methods, the biopolymers may be cDNAs, RNAs, DNA fragments or genes.

A system for displaying a dendrogram according to the present invention comprises: a clustering processor for clustering a plurality of types of biopolymers based on a set of data obtained by experiments of the plurality of biopolymers under different conditions, and analyzing the results thereof to display them in a dendrogram format; a display section for displaying the dendrogram; input means; and a keyword dictionary file for storing keywords of biopolymer information. The input means may be a keyboard or a mouse which is used for selecting a branch in the dendrogram, selecting a clustering method and the like. The keyword dictionary file may be used to evaluate whether the results of clustering have turned out to be successful.

This system for displaying a dendrogram may have a function of displaying a subtree selected by the input means on a separate window. Alternatively, the system may have a function of designating a different clustering method for the subtree displayed on the separate window to cluster the biopolymers included in the subtree again according to the designated clustering method, and displaying the results thereof in a dendrogram format.

The system for displaying a dendrogram may have a function of replacing the subtree selected by the input means with an icon, and a function of restoring the subtree icon to the original subtree in the dendrogram format.

The system for displaying a dendrogram may have a function of counting and displaying the number of biopolymers containing in their biopolymer information a keyword from a keyword dictionary file, and/or a function of displaying a location of a biopolymer in the dendrogram, which includes the designated keyword.

According to the system for displaying a dendrogram of the invention, the biopolymers may be DNAs, RNAs, DNA fragments or genes.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a diagram showing an exemplary display of results of a standard clustering analysis.

Figure 2 is a diagram showing an example of difference between clustering methods.

Figure 3 is a diagram showing exemplary dendrograms with normalized distance (dissimilarity) obtained by different clustering methods.

Figure 4 is a diagram showing an exemplary dendrogram including a gene group with similar expression patterns.

Figure 5 is a view showing an exemplary display screen according to a dendrogram displaying system of the invention.

Figure 6 is a view showing another exemplary display screen according to a dendrogram displaying system of the invention.

Figure 7 is a view showing yet another exemplary display screen according to a dendrogram displaying system of the invention.

Figure 8 is a view showing still yet another exemplary display screen according to a dendrogram displaying system of the invention.

Figure 9 is a schematic view showing an exemplary configuration of a dendrogram displaying system of the invention.

Figure 10 is a diagram showing exemplary gene expression pattern data.

Figure 11 is a diagram showing an exemplary gene information structure.

Figure 12 is a diagram showing an exemplary cluster structure.

Figure 13 is a diagram showing an example for generating a cluster tree structure.

Figure 14 is a diagram showing an exemplary array for storing distances between clusters.

Figure 15 is a diagram showing an exemplary array for storing root nodes of respective windows.

Figure 16 is a diagram showing an example of a structure for storing a query of search and its results.

Figure 17 is a flowchart showing a general process of the present system.

Figure 18 is a flowchart showing a process of reading out gene data.

Figure 19 is a flowchart showing a process for clustering analysis.

Figure 20 is another flowchart showing a process for clustering analysis.

Figure 21 is a flowchart showing a process for replacement/restoration of icon.

Figure 22 is a flowchart showing a process of searching in gene information

Figure 23 is a flowchart showing a process of searching for a keyword (Process A).

Figure 24 is a flowchart showing a process of reading out gene data of a subtree.

Figure 25 is a flowchart showing a process of generating a new cluster for a leaf of a subtree (Process B).

DESCRIPTION OF THE PREFERRED EMBODIMENTS

Hereinafter, the present invention will be described by way of examples with reference to the accompanying drawings. Although genes are exemplified as a subject of clustering in the following examples, the present invention is not limited thereto and is also applicable to other general biopolymers such as cDNAs, RNAs and DNA fragments.

Figure 9 is a schematic view showing a configuration of an exemplary system for displaying a dendrogram according to the invention. The system is provided with gene data 901 for storing gene information and gene expression patterns, a clustering processor 902 for clustering based on the gene

expression patterns, and analyzing and displaying the results in a dendrogram format, a display device **903** on which the dendrogram is displayed, input means such as a keyboard **904** and a mouse **905** for selecting a branch in the dendrogram or for selecting a clustering method, and a keyword dictionary file **906** for storing keywords of gene information to provide means for evaluating whether the results of clustering are in a user's desired form. The clustering processor **902** is realized with a computer and a program thereof. In stead of the storage medium **901**, gene data can be acquired from a database managed by a remote server computer communicating with the system via a network or the like.

Figure **10** is a schematic view showing a specific structure of gene expression pattern data stored in the gene data **901**. According to the present algorithm, the data is stored as a two-dimensional array. Specifically, numerated data of an expression level (brightness of hybridized fluorescent signal) of a gene corresponding to gene ID **(id)** under an experiment case **(no)** is stored as **Exp[id][no]**. The results obtained from a DNA chip spotted with **m** numbers of genes at different positions correspond to a single experiment case.

Figure **11** is a diagram showing an example of a gene information structure for storing information of a gene stored in the gene data **901**. The gene structure includes members representing gene ID (1101), ORF of the gene (1102),

name of the gene (1103) and a function of the gene (1104). The example shown in Figure 11 is merely an example, and the gene information structure may include information other than the attributes mentioned in the figure.

Figure 12 is a diagram showing exemplary structures indicating clusters used in the clustering. Each cluster structure corresponds to either a node or a leaf in a dendrogram. Each of the cluster structures is managed in a window unit. Nodes or leaves in the same window are provided with the same window ID (1207). In order to identify nodes or leaves in the same window from each other, each cluster structure is uniquely assigned with a **clusterNo** (1205). There are three types of cluster structures, and the values of type (1201) may be **leaf**, **node** or **icon**.

A leaf-type cluster structure corresponds to a single gene ID (1206), i.e., a single gene. Based on the gene ID, data of the gene information structure can be referred. A node-type cluster structure is generated upon every joining step during the clustering. Based on this node-type cluster, the two clusters that have been joined can be referred to as **left** value (1202) and **right** value (1203), and the distance ((dis)similarity) therebetween is stored as **distance** value (1204). The **left** and **right** values are represented by **clusterNo** (1205). An icon-type cluster structure is generated upon replacing the subtree with an icon to be treated in the same manner as the leaves upon display. An

icon indicating the subtree is provided on the tip of the branch. An actual cluster at the root of the subtree can be referred to from the **left** value (**1202**).

Figure **13** is a diagram showing a data structure of the cluster structures exemplified in Figure **12**. The data structure is generated during the course of the clustering analysis. First, the cluster structures start with only leaf-type structures. Then, as clustering takes place, every two cluster structures are joined together upon which a node-type cluster structure is generated, thereby forming a tree structure. Each node-type cluster structure includes information of **clusterNo** of the two joined child nodes and the distance ((dis)similarity) therebetween. Relative gene information can be referred to based on gene ID registered in the leaf-type cluster structures. If a subtree is replaced with an icon, an icon-type cluster is inserted into the tree to be treated as a leaf (clusters downstream from the icon-type cluster are not displayed). For restoring the icon, clusters upstream and downstream from the icon-type cluster are rejoined).

Figure **14** is a diagram showing an example of an array for storing dissimilarity values (i.e., distances between clusters) during the course of the clustering analysis. As shown in the figure, dissimilarity values are stored as a two-dimensional array **dist[][]**. **clusterNo**(**1205**) of clusters corresponding to the indices of the two-dimensional array

dist[][] are stored in clust_idx[]. Specifically, the value of the dissimilarity dist[i][j] indicates a dissimilarity value between clusters whose clusterNo are clust_idx[i] and clust_idx[j]. For example, as can be appreciated from Figure 14, the value of dissimilarity dist[3][4] between clusterNo: 9 as clust_idx[3] and clusterNo: 25 as clust_idx[4] is 21.

Figure 15 is a diagram showing an example of an array for storing root nodes of respective windows. Specifically, the clusterNo of the cluster at the root node in each display window is stored in an array RootNode[]. In the example shown in Figure 15, the value of RootNode[1] is 569, which means that the root node of the dendrogram displayed on a display window corresponding to window ID:1 is a cluster of clusterNo: 569. Similarly, since the value of RootNode[2] is 312, the root node of the dendrogram displayed on a display window corresponding to window ID: 2 is a cluster of clusterNo: 312.

Figure 16 is a diagram showing an example of a search structure for storing a query of search and its results. For each keyword registered in the keyword dictionary file 906, a single structure is generated. When some of synonyms are included in the keywords, they can be processed as a single search target. The search structure includes members such as keyword (1601) for registering a keyword as a search target, times (1602) indicating the number of the keyword contained in the subtree, place (1603) for storing locations of genes

on the dendrogram whose gene information include the keyword. As illustrated in Figure 16, synonyms such as **Rat**, **Mouse** and **Mus** can collectively be registered in the **keyword** member so that these three keywords can be treated as an identical search target.

Figure 17 is a flowchart of a general process of the present system.

First, data is read out from the gene data **901** to the clustering processor **902** (Step **1701**), which will be described later in more detail. Then, various parameters required for carrying out a clustering analysis and displaying results are set (Step **1702**). In the present example, a grouping algorithm, a type of (dis)similarity, and whether or not gene information should be displayed are determined.

Next, a clustering analysis takes place (Step **1703**), and the results thereof are displayed (Step **1704**). Detail of the clustering analysis will be described later. During this clustering analysis, information necessary for displaying a dendrogram is collected and input into cluster structures. The results of the analysis are displayed based on these cluster structures and the information of **RootNode[]** indicating the **clusterNo** of the root nodes on respective window. When the cluster structure is of an icon-type, it is processed as a leaf, and an icon representing a subtree is provided at the tip of the branch.

When the subtree in the displayed dendrogram should be

simplified as an icon, or when the icon is to be restored to the original subtree, the following process is conducted (Step 1705). A branch in the dendrogram is selected with a mouse (Step 1706), and the corresponding subtree is replaced with the icon or an icon is restored to a subtree (Step 1707). Replacement and restoration processes will be described later in detail. Thereafter, the results of the analysis are displayed again (Step 1704).

When search should be conducted in the displayed dendrogram based on a keyword stored in the keyword dictionary file 906, the following process is carried out (Step 1708). A branch in the dendrogram is selected with a mouse (Step 1709), and search is performed (Step 1710). The detail of the search will be described later. Since information required for display will be stored in search structures by searching process 1710, a search results window is newly generated based on the search structures to display the results (Step 1711). By selecting a keyword in the search results window with a mouse or the like, the location(s) of the keyword on the dendrogram is(are) marked based on the information of the place member(s) of the search structures.

When clustering based on another combining algorithm or (dis)similarity type should be conducted to the displayed dendrogram, the process returns to Step 1702 (Step 1712). Examples of cluster-combining algorithm include nearest

neighbor method, furthest neighbor method, group average method, centroid method, median method, Ward method and flexible method. According to the nearest neighbor method, the furthest neighbor method, the group average method, the Ward method and the flexible method, dissimilarity simply becomes larger as clusters are merged. As two clusters are merged into one, the merged cluster may become closer to or farther from other clusters. The former is referred to as space contraction, and the latter is referred to as space expansion. A case where the distance is unchanged is referred to as space preservation. The nearest neighbor method has a characteristic of space contraction, and the furthest neighbor method and Ward method each have a characteristic of space expansion. The group average method, the centroid method and the median method each have a characteristic of space preservation. The flexible method may have any of the space characteristics depending on parameter settings. There are various types of (dis)similarity. Typical examples of dissimilarity include squared Euclidean distance, standardized squared Euclidean distance, Mahalanobis' general distance and Minkowsky distance. An appropriate dissimilarity can be selected among the above-mentioned distances considering the above-described characteristic and the like.

When a subtree in the displayed dendrogram should be displayed on a separate window (Step 1713), a branch to be

displayed on the separate window is selected in the dendrogram with a mouse (Step 1714). Then, data corresponding to the selected subtree in the dendrogram is read out (Step 1715), and the process returns to Step 1702. Process of reading out data corresponding to the selected subtree will be described later in detail. When no further selection is to be made, the whole process is ended.

Figure 18 is a detailed flowchart of the reading out process 1701 in Figure 17.

First, the total numbers of genes and experiment cases are registered in **gene_num** and **exp_num**, respectively (Step 1801). Then, gene information is read out from the gene data 901 to be registered in gene information structures **gene_info[i]** (where i = 1, ..., **gene_num**) (Step 1802). Gene expression data is read out from the gene data 901 to be registered in **Exp[i][j]** (where i = 1, ..., **gene_num**, and j = 1, ..., **exp_num**) (Step 1803). Then, **gene_num** is input into **leaf_num** indicating the total number of leaves in the dendrogram (Step 1804).

Next, leaf-type cluster structures are generated as initial values. The **leaf_num** number of cluster structures are generated. And for i = 1, ..., **leaf_num**, **type** member, **clusterNo**, **geneID** and **windowID** are set to **leaf**, i, i and 1 respectively (Step 1805). Then, keywords stored in the keyword dictionary file 906 are read out. For each keyword, a search structure is generated, and the keyword is

registered as search[].keyword (Step 1806). The total number of keywords is substituted for key_num (Step 1807). wid representing window ID is set to 1 (Step 1808), and the process is ended.

Figures 19 and 20 are detailed flowcharts of clustering analysis process 1703 in Figure 17.

Dissimilarity between expression levels of genes displayed on the window whose window ID corresponds to wid is calculated. Dissimilarity between genes of clusterNo i and clusterNo j is registered as dist[i][j] (Step 1901). According to the present algorithm, clusterNo is sequentially assigned every time a cluster is generated starting from 1. Accordingly, for a next cluster to be generated, leaf_num+1 is substituted for newclusterNo as the number of the next cluster (Step 1902). As array information for storing distances (dissimilarity) between clusters, leaf_num is substituted for all_clust representing the number of clusters to be joined, and for i = 1, ..., leaf_num, i is substituted for cluster_idx[i] for initialization. The number of the clusters to be joined (all_clust) is evaluated as to whether or not it equals to 1. When it does not equal to 1, the following processes are repeated until it equals to 1 (Step 1905).

First, based on the previously determined distance (dissimilarity) between clusters, clusters to be joined next are determined. For $i < j$ and $i, j = 1, 2, \ldots,$ all_clust, a

minimum value of **dist[i][j]**, and i and j that give the minimum value are obtained to substitute for **d_min**, **i_min** and **j_min**, respectively. Clusters to be joined next are clusters of **clusterNo** represented by **cluster_idx[i_min]** and **cluster_idx[j_min]**. A cluster is newly generated, and **type**, **left**, **right**, **distance**, **clusterNo** and **windowID** are set to **node**, **cluster_idx[i_min]**, **cluster_idx[j_min]**, **d_min**, **newclusterNo** and **wid**, respectively (Step 1907). Which one of the clusters should be assigned as **left** member and the other as **right** member may be determined by providing a predetermined criterion such as comparison of expression levels.

Then, information of the array storing distances between clusters is updated. First, a distance ((dis)similarity) between a newly generated cluster and other cluster is calculated and overwritten on a location of array **dist[][]** where a distance between a cluster corresponding to **i_min** and other cluster is stored. For **i** = 1, 2, ..., **i_min** - 1, dissimilarity between the newly generated cluster and a cluster whose **clusterNo** corresponds to **cluster_idx[i]** is registered in **dist[i][i_min]** (Step 2001). For **j** = **i_min+1**, ..., **J_min-1**, **j_min+1**, ..., **all_clust**, dissimilarity between the newly generated cluster and a cluster corresponding to **cluster_idx[j]** is registered as **dist[i_min][j]** (Step 2002).

Next, information relative to **j_min** is deleted and all of the array data following j_min is shifted forward. For i

= j_min, ..., all_clust-1, clust_idx[i+1] is substituted for clust_idx[i] (Step 2003). Then, for i and j that satisfy i < j and i, j = j_min, ..., all_clust, dist[i+1][j] is substituted for dist[i][j] (Step 2004). Thereafter, for i and j that satisfy i < j, i = 1, ..., all_clust-1 and j = j_min, ..., all_clust-1, dist[i][j+1] is substituted for dist[i][j] (Step 2005).

Finally, 1 is subtracted from all_clust indicating the number of clusters to be joined (Step 2006). NewclusterNo indicating clusterNo assigned to a new cluster structure is added with 1 (Step 2007).

The above-described process is repeated until all_clust becomes 1. When all_clust becomes 1, cluster_idx[1] indicating clusterNo of a root node of the present window is substituted for RootNode[wid] (Step 1908) and the process is ended.

Figure 21 is a detailed flowchart of process 1707 in Figure 17 for replacement and restoration of an icon.

Clusters corresponding to both ends of the branch selected at Step 1706 are registered. The downstream (leaf side) cluster is substituted for childClust and the upstream (root side) cluster is substituted for parentClust (Steps 2101 and 2102). Then, a new icon-type cluster is generated and inserted between the childClust and parentClust. Specifically, a cluster is generated, where type, left, clusterNo and windowID are set to icon, childClust.clusterNo,

newclusterNo and wid, respectively (Step 2103). To re-link the pointer, clusterNo of childClust registered in either parentClust.left or parentClust.right is replaced with newclusterNo (Step 2104). As the total number of clusters will be increased by one, newclusterNo is added with 1 to indicate clusterNo assigned to a new cluster structure (Step 2105). Then, the process is ended.

When restoration of the subtree icon is selected from the menu, first, clusters corresponding to both ends of the branch selected at Step 1706 in Figure 17 are registered. The cluster of the icon downstream from (on the leaf side of) the branch selected at Step 1706 and the cluster at the parent node of the icon are substituted for iconClust and parentClust, respectively (Steps 2101 and 2106). The pointer linking the cluster of the icon is re-linked to the clusters of the subtree, and the cluster of the icon is deleted. Specifically, clusterNo of iconClust registered in either parentClust.left or parentClust.right is changed into iconClust.left (Step 2107). Then, iconClust is deleted (Step 2108) and the process is ended.

Figure 22 is a detailed flowchart of searching process 1710 in Figure 17.

First, clusterNo of a cluster at a root node of a subtree downstream from the selected branch is substituted for clustNo (Step 2201). Then, leafNo indicating an index assigned from the beginning of the leaves in the subtree is

initialized to 1 (Step 2202). For i = 1, ..., **key_num**, **search[i].times** and **search[i].place** are initialized to 0 and null, respectively (Step 2203). Then, treewalk is recursively performed on the cluster tree to search for a gene having the keyword designated in **search** (Process A) (Step 2205). Here, **clustNo** and **leafNo** are given as arguments. The detail of keyword searching process will be described later in detail. After Process A, the search results are input into the search structure and the process is ended.

Figure 23 is a detailed flowchart of keyword searching process (Process A) in Figure 22.

The given arguments **clustNo** and **leafNo** are substituted for **clustNo** and **leafNo**, respectively (Step 2300). The cluster corresponding to **clusterNo** is substituted for **targetClust** (Step 2301). A counter i for keyword search is set to 0 (Step 2302).

Then, **targetCluster.type** is evaluated as to whether it is **leaf** or not (Step 2303). When it is **leaf**, the following process is repeated until gene information corresponding to **leaf** is completely compared with the keyword read out from the keyword dictionary file. In other words, the process is repeated until i becomes **key_num** (Step 2304). First, the attribute of gene information structure **gene_info** corresponding to **targetClust.geneID** is evaluated as to inclusion of keyword **search[i].keyword** (Step 2305). If the keyword is included, **search[i].times**, which indicates the

number of detection of the keyword (search[i].keyword) in the subtree, is increased by 1. Then, leafNo of the detected location is registered in search[i].place indicating the index of the detected location in the subtree (Step 2307). The counter i for keyword search is increased by 1 and the process returns to Step 2304. When i becomes key_num at Step 2304, i.e., when entire keywords are completely compared, leafNo as an index of the subtree is increased by 1 (Step 2309) and the process is ended.

When targetCluster.type is not leaf at Step 2303, a child node is traced. First, targetClust.left is substituted for clustNo (Step 2310), and the keyword searching process (Process A) is performed on left child node using clustNo and leftNo as arguments (Step 2311). When targetCluster.type is icon, targetCluster.right has no child node (Step 2312) and thus the process is ended. When targetCluster.type is not icon at Step 2312, the cluster is of a node type. Thus, targetClust.right is substituted for clustNo (Step 2313), and keyword searching process (Process A) is repeated on the right child node using clustNo and leafNo as arguments (Step 2314) and the process is ended.

Figure 24 is a detailed flowchart of process 1715 in Figure 17, for reading out gene data of the subtree.

Since a subtree is newly read out and a window is newly generated, wid indicating a new window ID is increased by 1 (Step 2401). In addition, leaf_num indicating the total

number of leaves in the dendrogram is initialized to 0 (Step 2402). Then, clusterNo of a cluster at the root node of the subtree downstream from the selected branch is substituted for clusterNo (Step 2403). Finally, process of generating new cluster (Process B) is performed on the leaf-type cluster of the subtree (Step 2404). For this process, clustNo indicating the present cluster is given as an argument. This process will be described later in detail. After reading out all leaves and generating all clusters corresponding to the leaves, the process is ended.

Figure 25 is a detailed flowchart of process 2404 in Figure 24, for generating a new cluster corresponding to a leaf in the subtree.

The given argument clustNo is registered as clustNo, and the cluster indicated by the given clustNo is set as targetClust (Steps 2501 and 2502). Then, targetCluster.type is evaluated as to whether it is leaf or not (Step 2503). If it is leaf, leaf_num as a counter of the number of leaves of the subtree is increased by 1 (Step 2504). Then, a leaf-type cluster structure is generated as an initial value of the new window. Specifically, a cluster is generated where type, clusterNo, geneID and windowID are set to leaf, leaf_num, targetCluster.geneID and wid, respectively, thereby ending the process (Step 2505).

When targetCluster.type is not leaf at Step 2503, a child node is traced. First, targetClust.left is substituted

for clustNo (Step 2506), and a cluster is newly generated again using clustNo as an argument (Process B) (Step 2507). When targetCluster.type is icon, targetCluster.right has no child node, and thus the process is ended (Step 2508). When targetCluster.type is not icon at Step 2508, the cluster is of a node type. Accordingly, targetClust.right is substituted for clustNo (Step 2509), and a new cluster generating process (Process B) is repeated for the right child node using clustNo as an argument and the process is ended (Step 2510).

Herein, the result of the analysis is displayed only on a display device. However, the results can be printed out with a multicolor printer. According to the present invention, the idea of display also comprises a printed out display.

According to the present invention, a method for aiding gene expression analysis or the like is provided, where various clustering methods can be applied to a dendrogram, and a subtree can be replaced with an icon or displayed on a separate window.

Claims

1. A method for displaying a dendrogram comprising the steps of:

clustering a plurality of types of biopolymers based on a set of data obtained by experiments of the plurality of biopolymers under different conditions, and displaying the results thereof in a dendrogram format;

selecting a subtree in the dendrogram; and

displaying the selected subtree on a separate window.

2. A method for displaying a dendrogram according to claim 1, further comprising the steps of:

designating a different clustering method for the biopolymers included in the subtree displayed on the separate window; and

clustering the biopolymers included in the subtree again according to the designated clustering method, and displaying the results thereof in a dendrogram format.

3. A method for displaying a dendrogram comprising the steps of:

clustering a plurality of types of biopolymers based on a set of data obtained by experiments of the plurality of biopolymers under different conditions, and displaying the results thereof in a dendrogram format;

selecting a subtree in the dendrogram; and

replacing the selected subtree with an icon.

4. A method for displaying a dendrogram according to claim 3, further comprising a step of restoring the subtree icon to the original dendrogram subtree format.

5. A method for displaying a dendrogram comprising the steps of:

clustering a plurality of types of biopolymers based on a set of data obtained by experiments of the plurality of biopolymers under different conditions, and displaying the results thereof in a dendrogram format;

selecting a subtree in the dendrogram; and

from the biopolymers included in the selected subtree, counting and displaying the number of biopolymers containing in their biopolymer information a keyword from a keyword dictionary file.

6. A method for displaying a dendrogram comprising the steps of:

clustering a plurality of types of biopolymers based on a set of data obtained by experiments of the plurality of biopolymers under different conditions, and displaying the results thereof in a dendrogram format;

selecting a subtree in the dendrogram;

designating a keyword; and

displaying a location of a biopolymer in the dendrogram, which includes the designated keyword in its biopolymer information.

7. A method for displaying a dendrogram according to any one of claims 1 to 6, wherein the biopolymers are cDNAs, RNAs, DNA fragments or genes.

8. A system for displaying a dendrogram comprising:

a clustering processor for clustering a plurality of types of biopolymers based on a set of data obtained by experiments of the plurality of biopolymers under different conditions, and analyzing the results thereof to display them in a dendrogram format;

a display system for displaying the dendrogram;

input means; and

a keyword dictionary file for storing keywords of biopolymer information.

9. A system for displaying a dendrogram according to claim 8, comprising a function of displaying a subtree selected by the input means on a separate window.

10. A system for displaying a dendrogram according to claim 9, comprising a function of designating a different clustering method for the subtree displayed on the separate window to cluster the biopolymers included in the subtree again according to the designated clustering method, and displaying the results thereof in a dendrogram format.

11. A system for displaying a dendrogram according to any one of claims 8 to 10, wherein the system comprises a function of replacing the subtree selected by the input means with an icon, and a function of restoring the subtree icon to the original subtree in the dendrogram format.

12. A system for displaying a dendrogram according to any one of claims 8 to 11, wherein the system comprises a function of counting and displaying the number of biopolymers containing in their biopolymer information a keyword from a keyword dictionary file, and/or a function of displaying a location of a biopolymer in the dendrogram, which includes the designated keyword.

13. A system for displaying a dendrogram according to any one of claims 8 to 12, wherein the biopolymers are cDNAs, RNAs, DNA fragments or genes.

Fig. 1

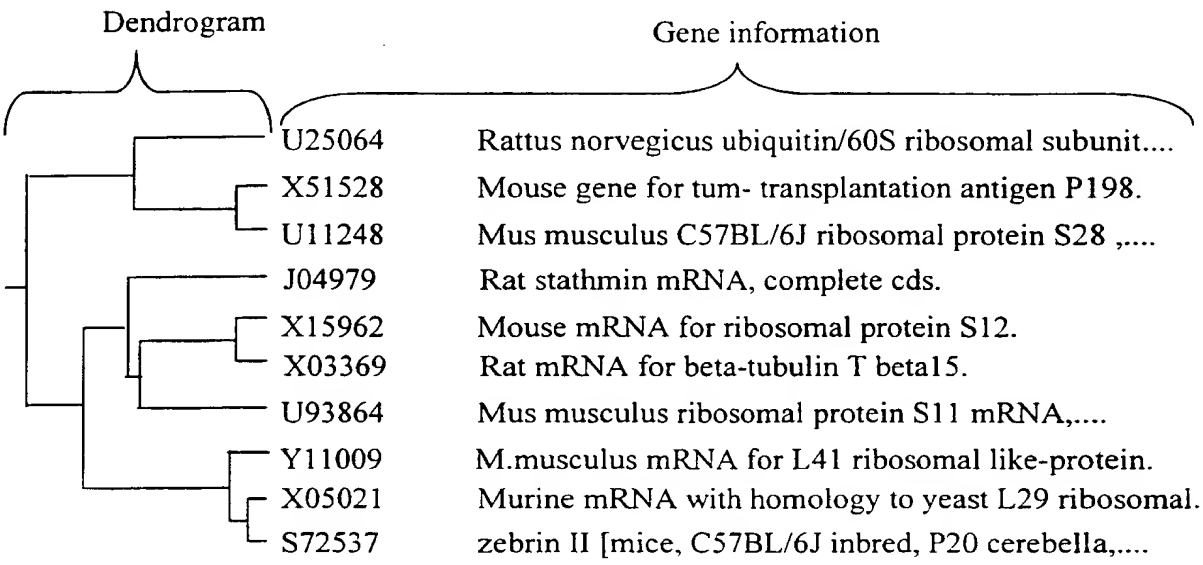

Dendrogram
Gene information
U25064
X51528
U11248
J04979
X15962
X03369
U93864
Y11009
X05021
S72537
Rattus norvegicus ubiquitin/60S ribosomal subunit....
Mouse gene for tum- transplantation antigen P198.
Mus musculus C57BL/6J ribosomal protein S28 ,....
Rat stathmin mRNA, complete cds.
Mouse mRNA for ribosomal protein S12.
Rat mRNA for beta-tubulin T beta15.
Mus musculus ribosomal protein S11 mRNA,....
M.musculus mRNA for L41 ribosomal like-protein.
Murine mRNA with homology to yeast L29 ribosomal.
zebrin II [mice, C57BL/6J inbred, P20 cerebella,....

Fig. 2

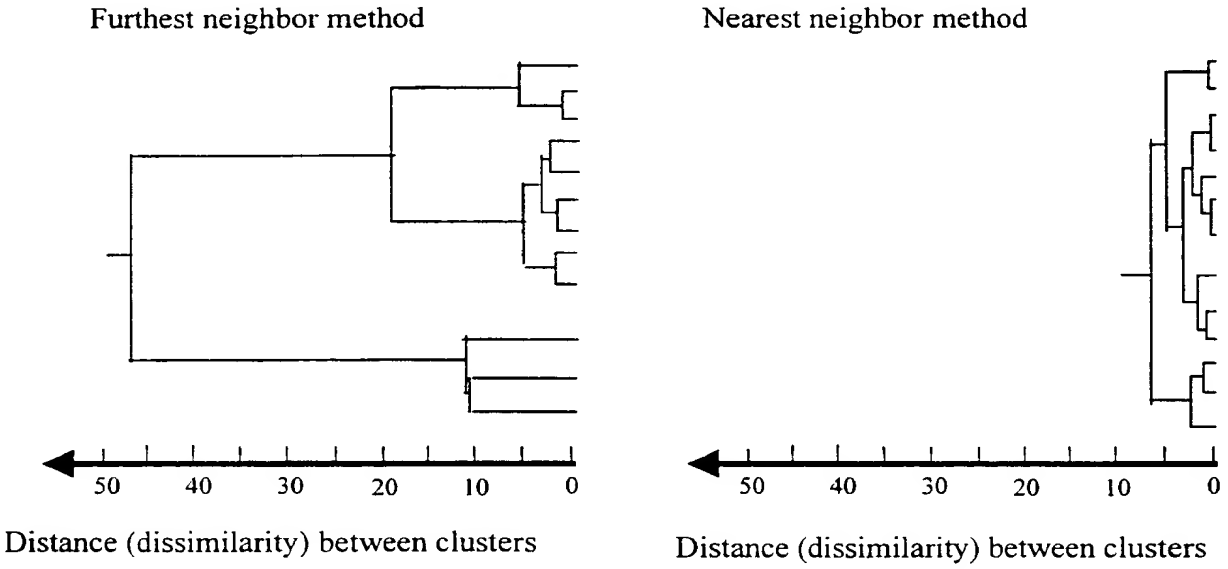

Furthest neighbor method
50
40
30
20
10
0
Distance (dissimilarity) between clusters
Nearest neighbor method
50
40
30
20
10
0
Distance (dissimilarity) between clusters

Fig. 3

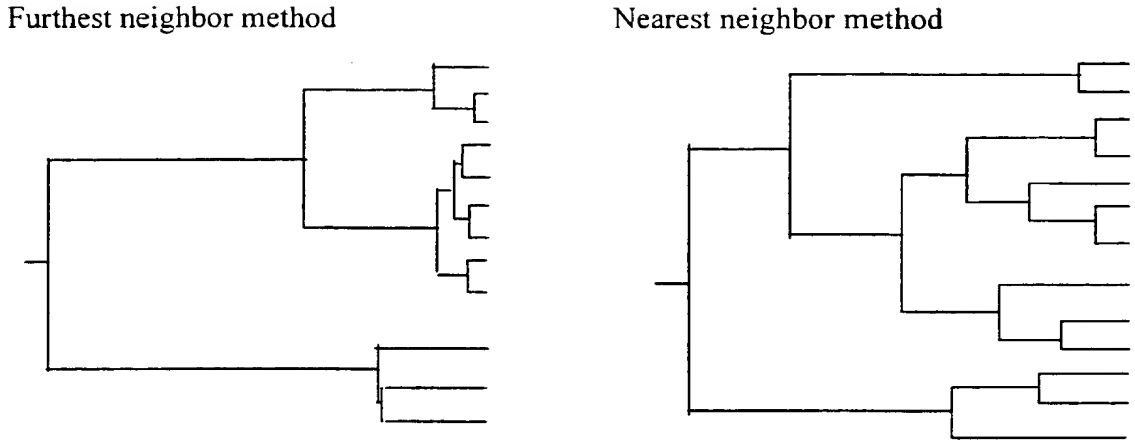

Furthest neighbor method
Nearest neighbor method

Fig. 4

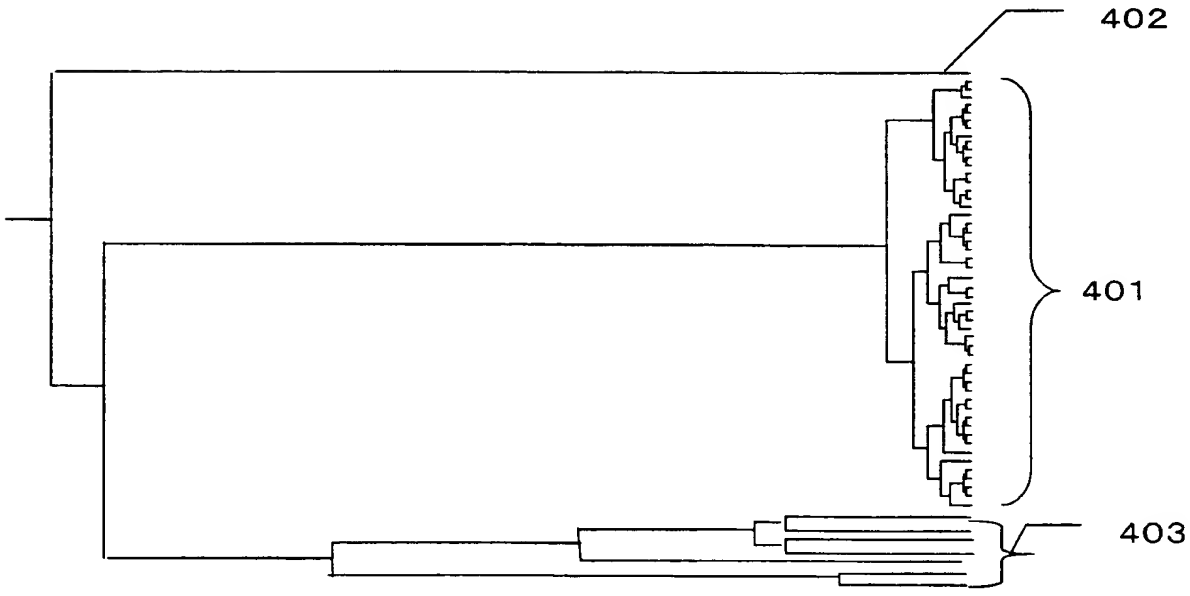

402
401
403

Fig. 5

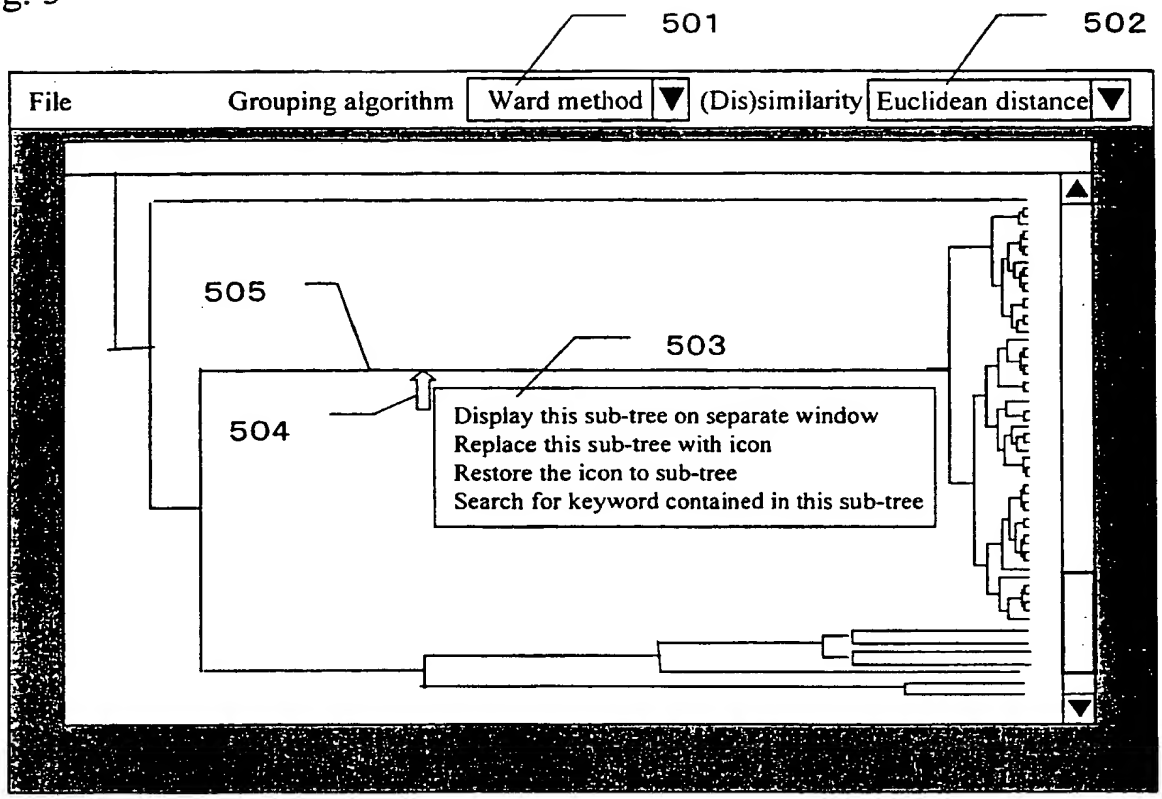

501
502
File
Grouping algorithm
Ward method
(Dis)similarity
Euclidean distance
505
503
504
Display this sub-tree on separate window
Replace this sub-tree with icon
Restore the icon to sub-tree
Search for keyword contained in this sub-tree

Fig. 6

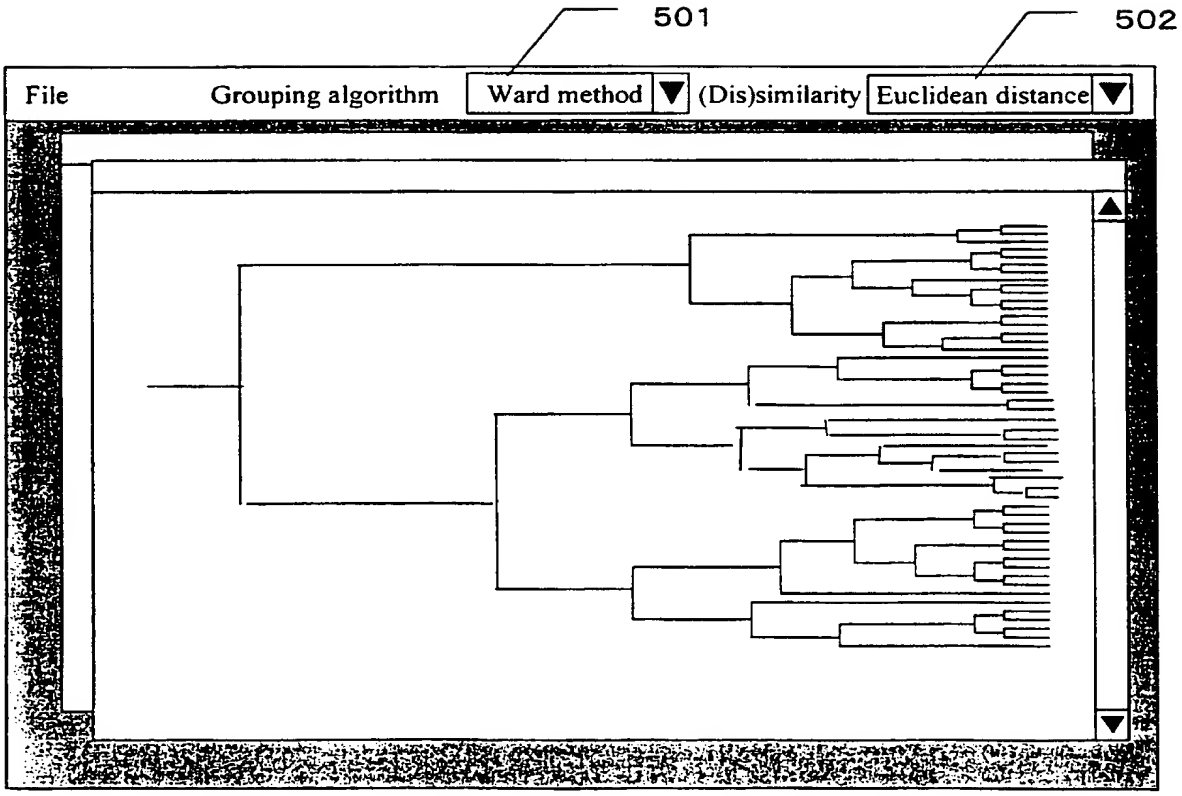

501
502
File
Grouping algorithm
Ward method
(Dis)similarity
Euclidean distance

Fig. 7

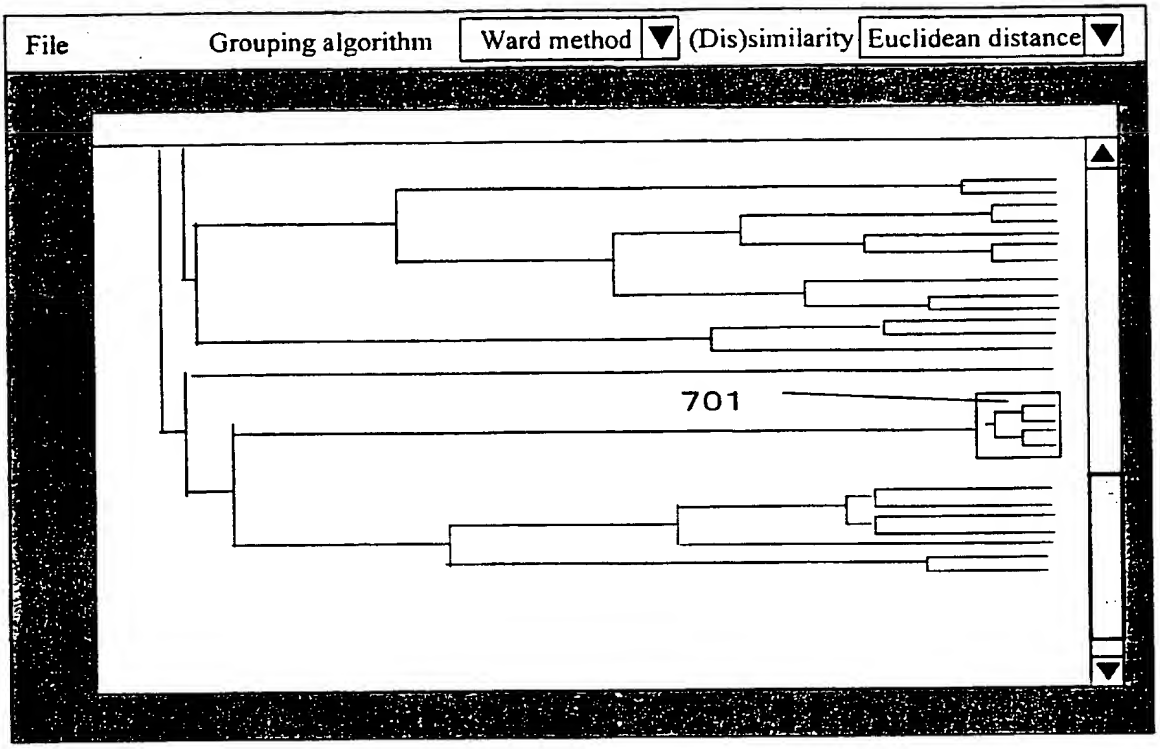

File
Grouping algorithm
Ward method
(Dis)similarity
Euclidean distance
701

Fig. 8

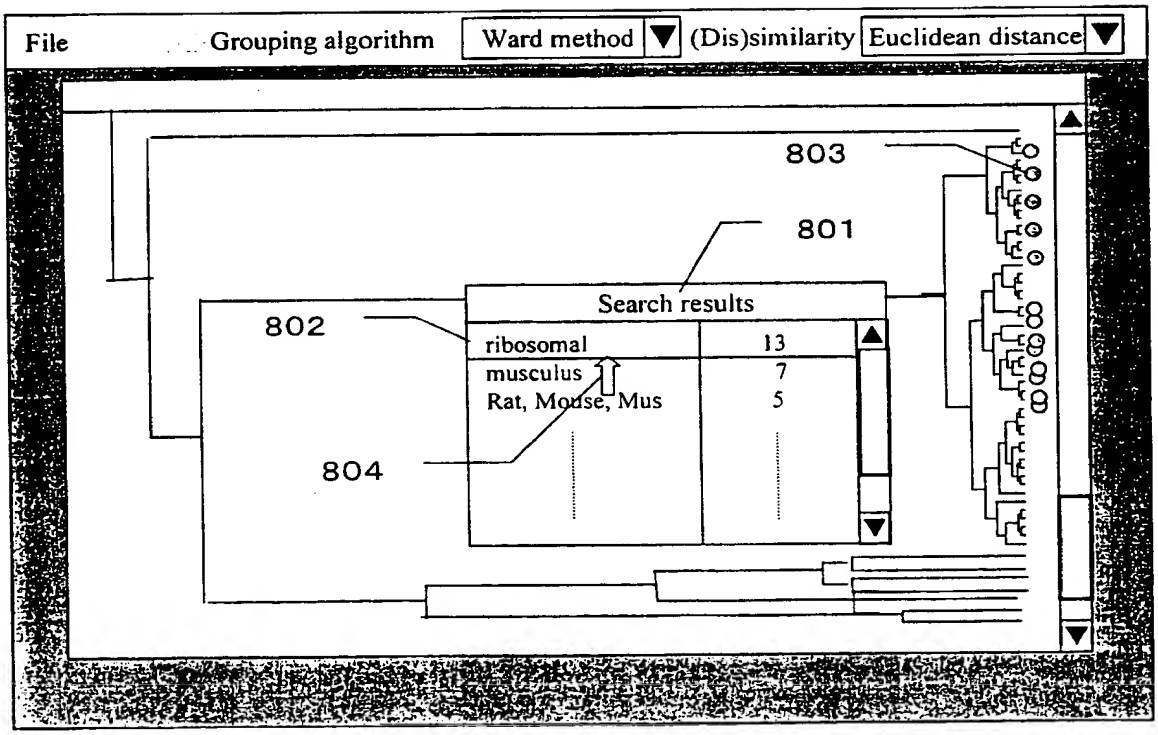

File
Grouping algorithm
Ward method
(Dis)similarity
Euclidean distance
803
801
Search results
802
ribosomal
13
musculus
7
Rat, Mouse, Mus
5
804

Fig. 9

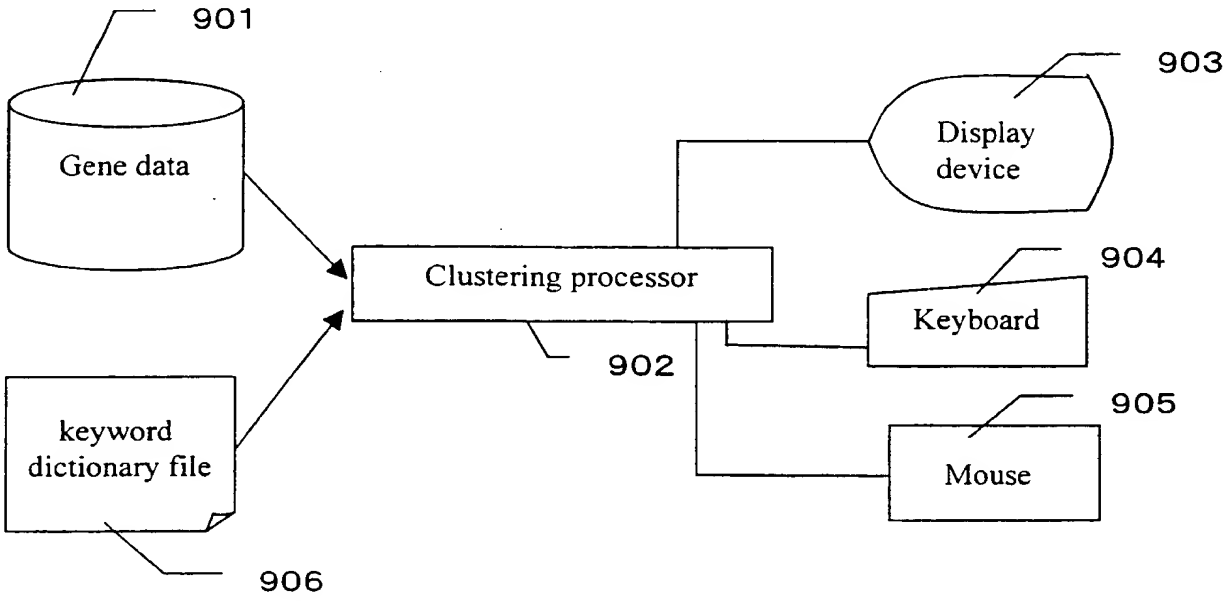

901
Gene data
903
Display device
Clustering processor
902
904
Keyboard
905
Mouse
keyword dictionary file
906

Fig. 10

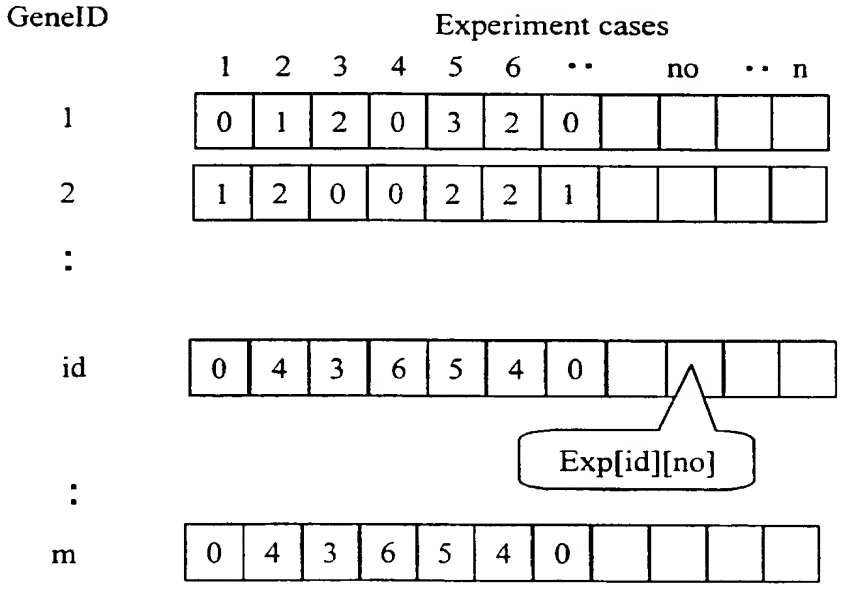

GeneID
Experiment cases
1 2 3 4 5 6 •• no •• n
1
0 1 2 0 3 2 0
2
1 2 0 0 2 2 1
:
id
0 4 3 6 5 4 0
Exp[id][no]
:
m
0 4 3 6 5 4 0

Fig. 11

gene_info

	Member	Value
1101	geneID	17
1102	ORF	YBL084C
1103	name	ANAPHASE-PROMOTING COMPLEX SUBUNIT
1104	function	CELL CYCLE

Fig. 12

cluster

	Member	Value
1201	type	leaf
1202	left	
1203	right	
1204	distance	
1205	clusterNo	17
1206	geneID	11
1207	windowID	3

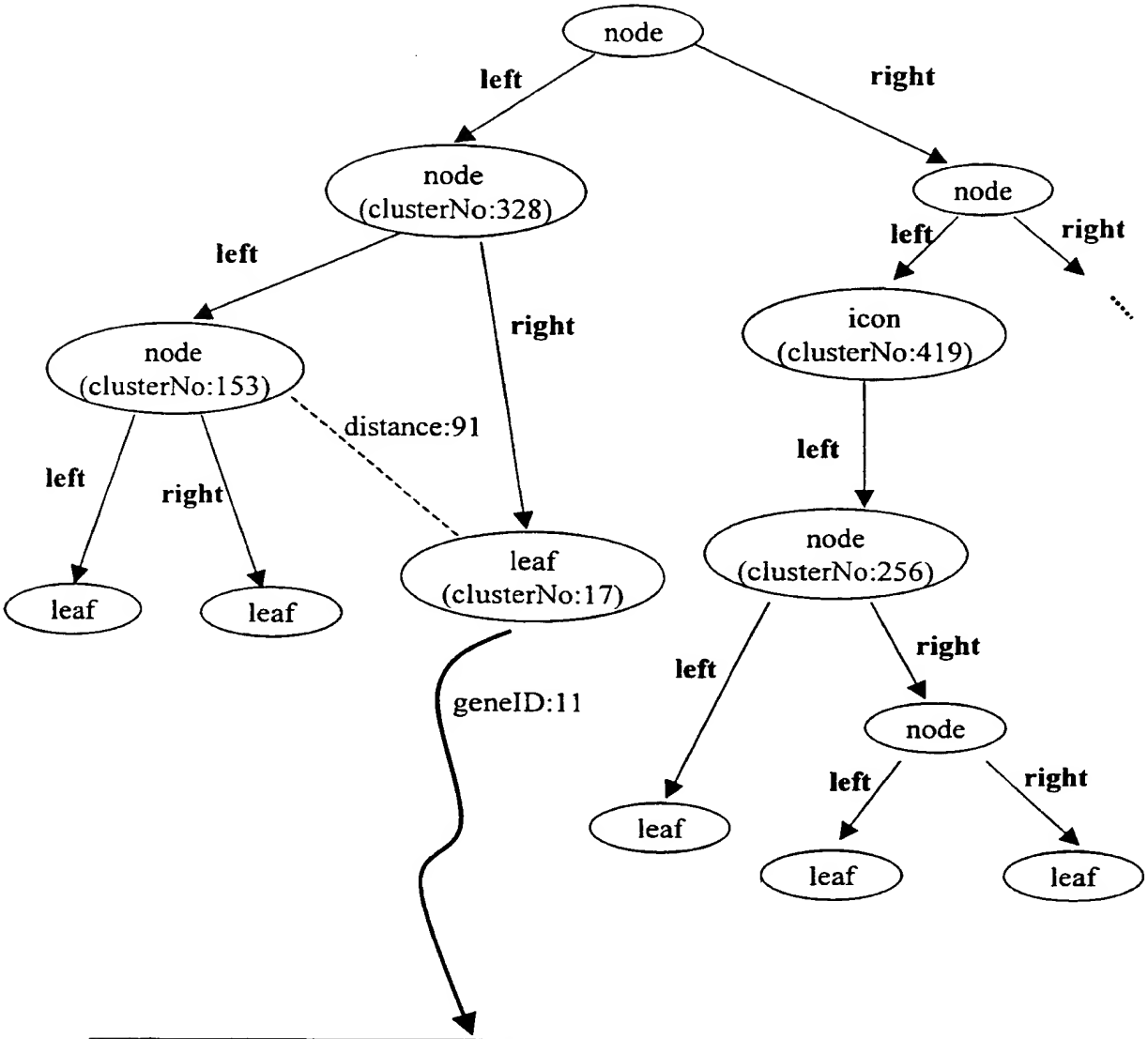
cluster

Member	Value
type	node
left	153
right	17
distance	91
clusterNo	328
geneID	
windowID	3

cluster

Member	Value
type	icon
left	256
right	
distance	
clusterNo	419
geneID	
windowID	3

Fig. 13



geneID	11
ORF	YDR342C
name	HEXOSE PERMEASE
function	TRANSPORT

Fig. 14

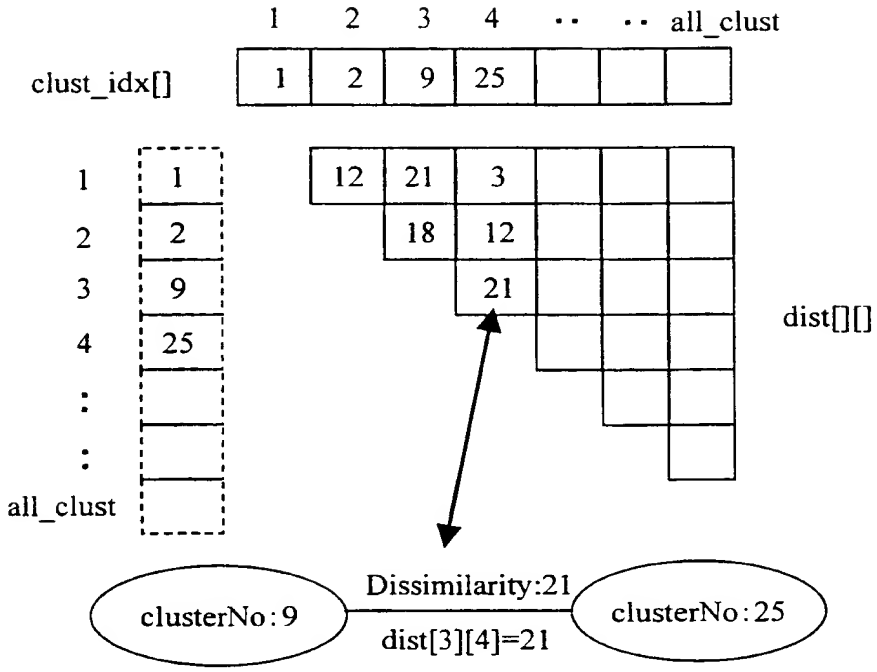

1 2 3 4 .. .. all_clust
clust_idx[]
1 2 9 25
1
2
3
4
:
:
all_clust
1
2
9
25
12 21 3
18 12
21
dist[][]
clusterNo:9
Dissimilarity:21
dist[3][4]=21
clusterNo:25

Fig. 15

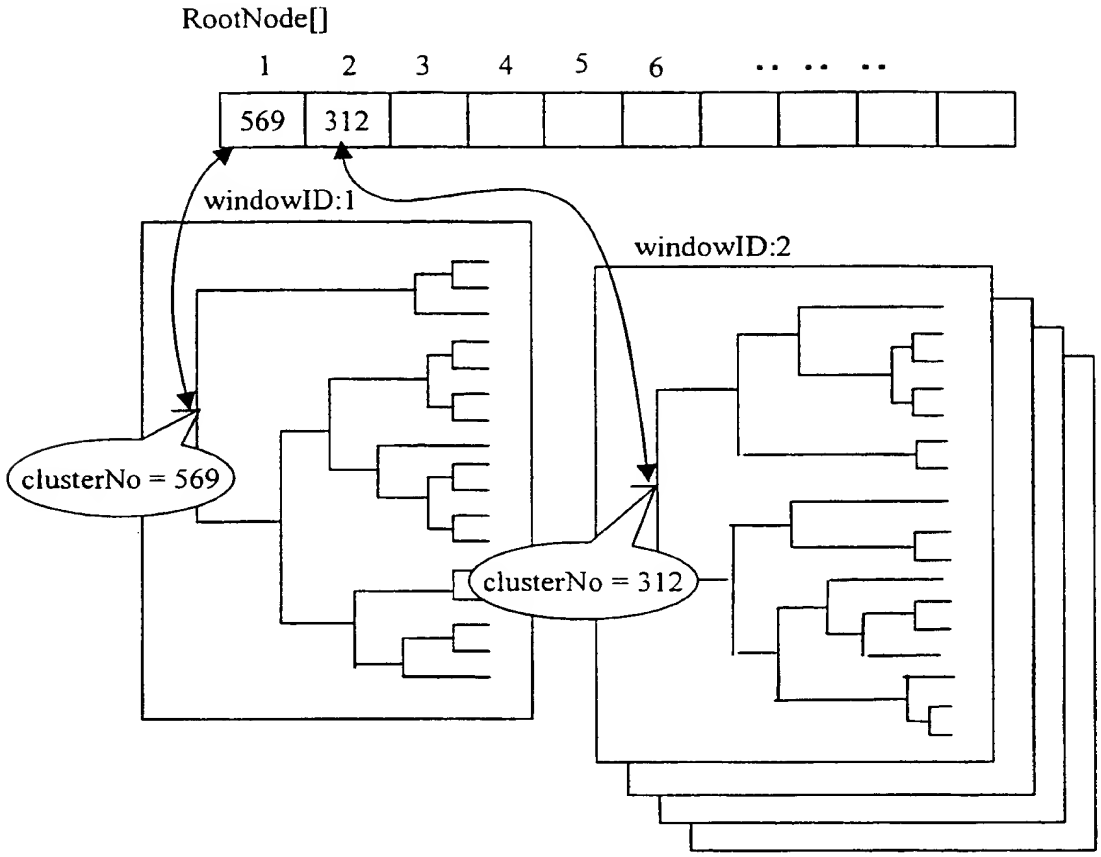

RootNode[]
1
2
3
4
5
6
569
312
windowID:1
windowID:2
clusterNo = 569
clusterNo = 312

Fig. 16

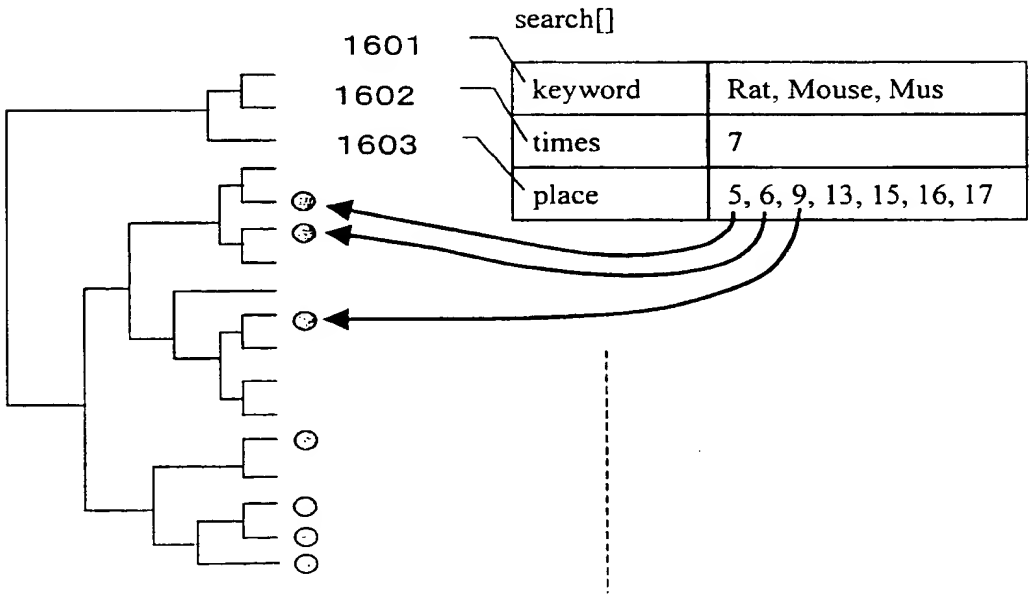

search[]
1601
1602
1603
keyword
Rat, Mouse, Mus
times
7
place
5, 6, 9, 13, 15, 16, 17

Fig. 17

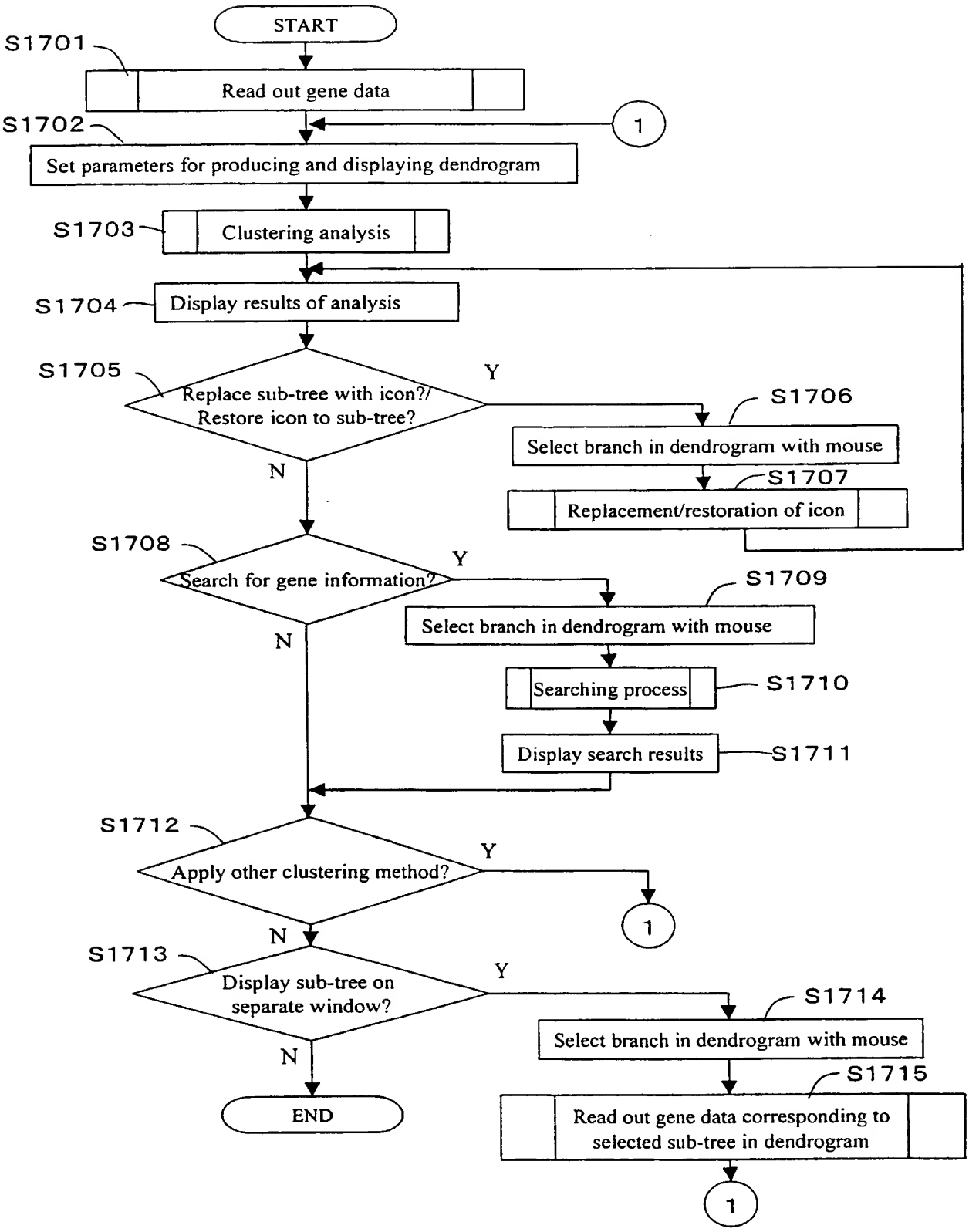

START
S1701
Read out gene data
S1702
1
Set parameters for producing and displaying dendrogram
S1703
Clustering analysis
S1704
Display results of analysis
S1705
Replace sub-tree with icon?/
Restore icon to sub-tree?
Y
S1706
Select branch in dendrogram with mouse
S1707
Replacement/restoration of icon
N
S1708
Search for gene information?
Y
S1709
Select branch in dendrogram with mouse
N
Searching process
S1710
Display search results
S1711
S1712
Apply other clustering method?
Y
1
N
S1713
Display sub-tree on
separate window?
Y
S1714
Select branch in dendrogram with mouse
N
S1715
END
Read out gene data corresponding to
selected sub-tree in dendrogram
1

Fig. 18

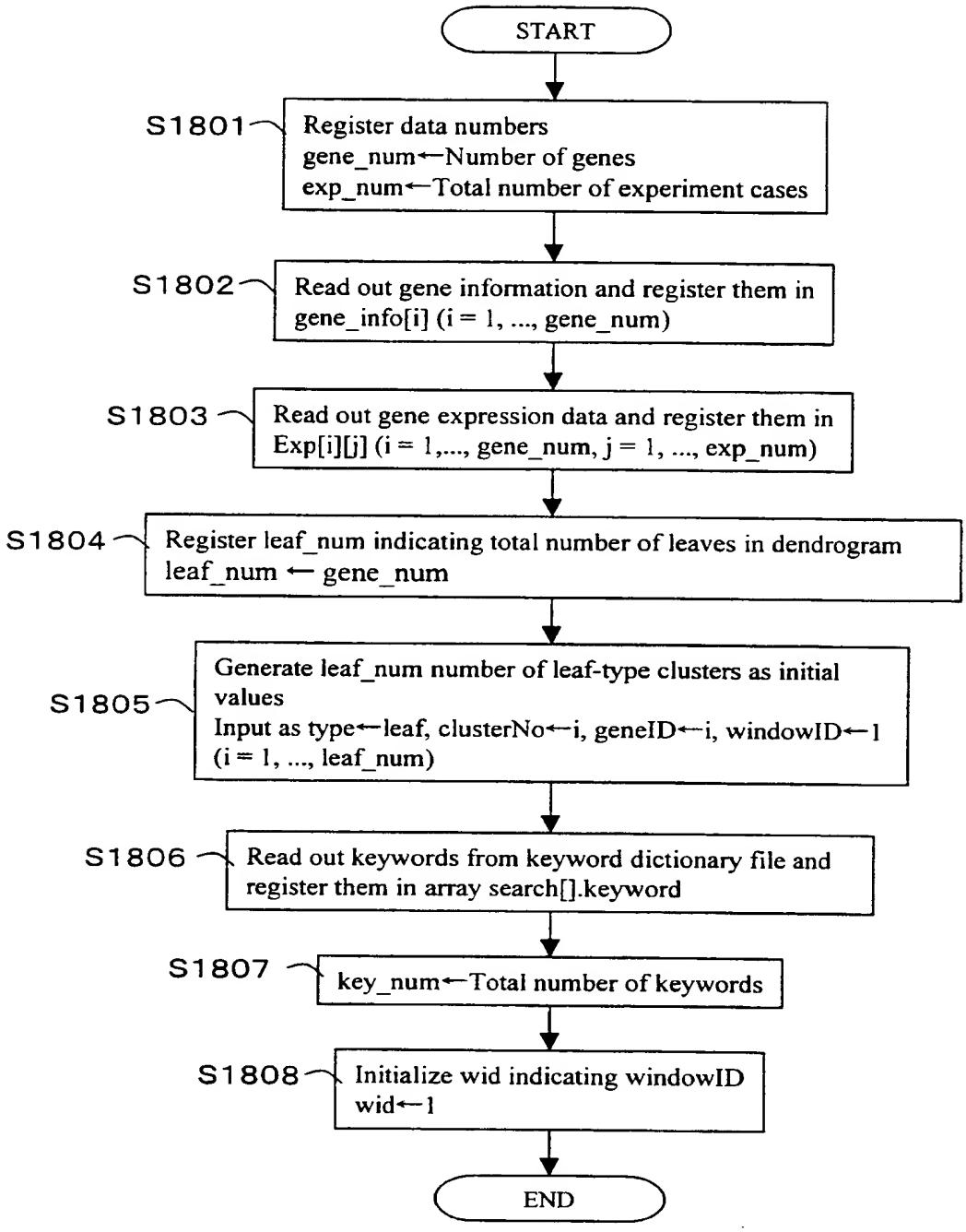

START
S1801
Register data numbers
gene_num←Number of genes
exp_num←Total number of experiment cases
S1802
Read out gene information and register them in
gene_info[i] (i = 1, ..., gene_num)
S1803
Read out gene expression data and register them in
Exp[i][j] (i = 1,..., gene_num, j = 1, ..., exp_num)
S1804
Register leaf_num indicating total number of leaves in dendrogram
leaf_num ← gene_num
S1805
Generate leaf_num number of leaf-type clusters as initial values
Input as type←leaf, clusterNo←i, geneID←i, windowID←1
(i = 1, ..., leaf_num)
S1806
Read out keywords from keyword dictionary file and register them in array search[].keyword
S1807
key_num←Total number of keywords
S1808
Initialize wid indicating windowID
wid←1
END

Fig. 19

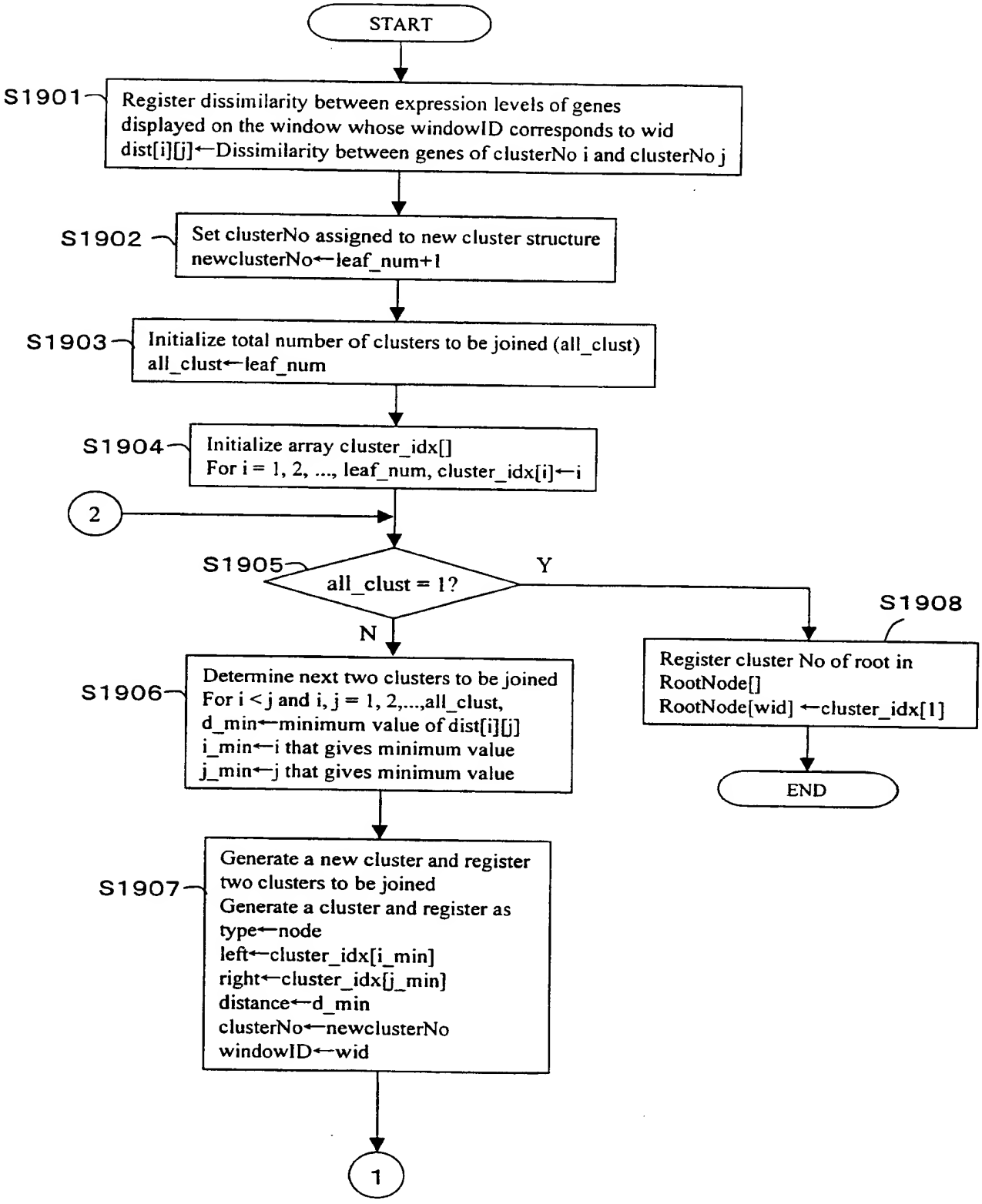

START
S1901
Register dissimilarity between expression levels of genes displayed on the window whose windowID corresponds to wid
dist[i][j]←Dissimilarity between genes of clusterNo i and clusterNo j
S1902
Set clusterNo assigned to new cluster structure
newclusterNo←leaf_num+1
S1903
Initialize total number of clusters to be joined (all_clust)
all_clust←leaf_num
S1904
Initialize array cluster_idx[]
For i = 1, 2, ..., leaf_num, cluster_idx[i]←i
2
S1905
all_clust = 1?
Y
N
S1908
Register cluster No of root in RootNode[]
RootNode[wid] ←cluster_idx[1]
END
S1906
Determine next two clusters to be joined
For i < j and i, j = 1, 2,...,all_clust,
d_min←minimum value of dist[i][j]
i_min←i that gives minimum value
j_min←j that gives minimum value
S1907
Generate a new cluster and register two clusters to be joined
Generate a cluster and register as
type←node
left←cluster_idx[i_min]
right←cluster_idx[j_min]
distance←d_min
clusterNo←newclusterNo
windowID←wid
1

Fig. 20

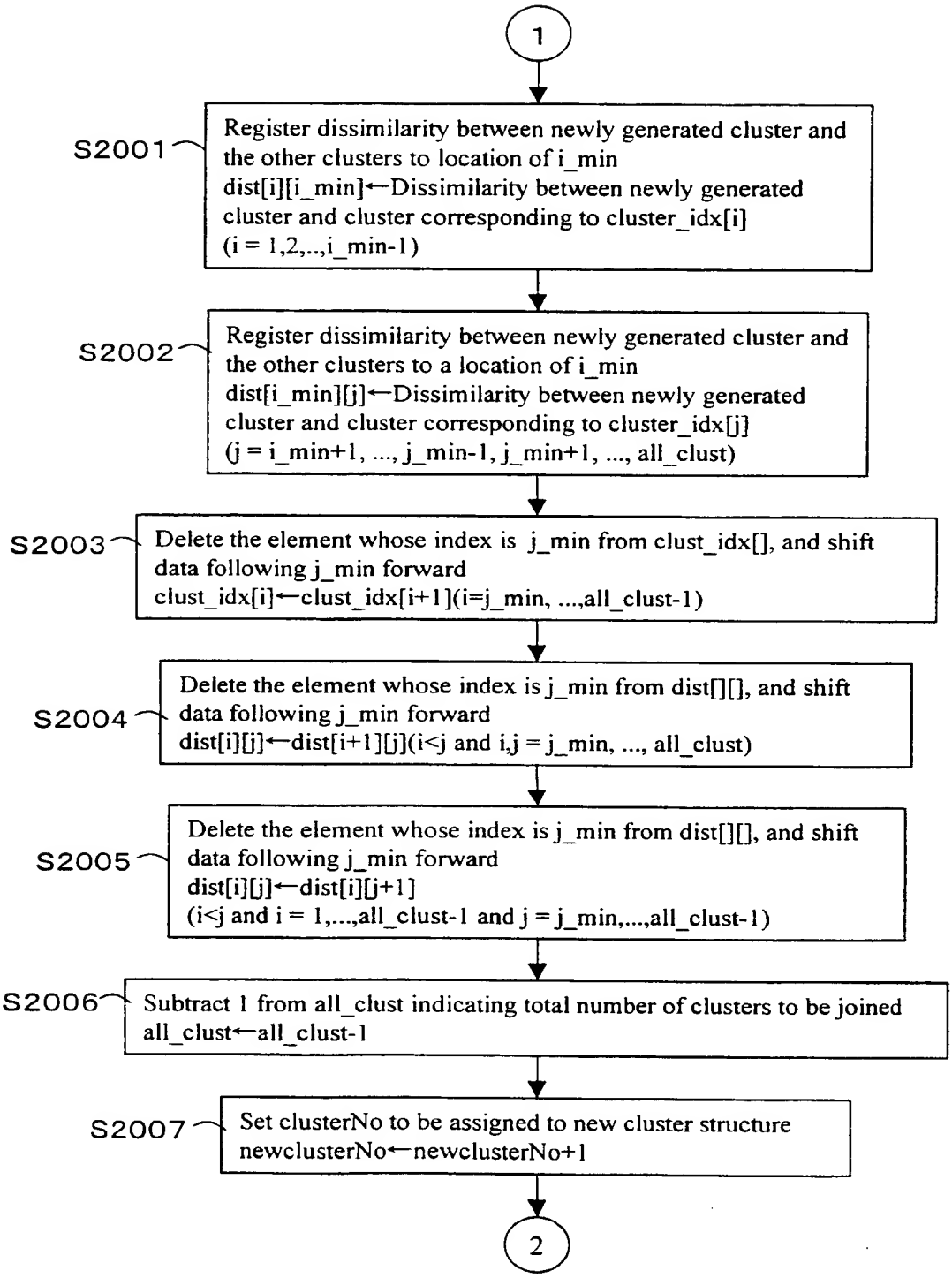

1
S2001
Register dissimilarity between newly generated cluster and the other clusters to location of i_min
dist[i][i_min]←Dissimilarity between newly generated cluster and cluster corresponding to cluster_idx[i]
(i = 1,2,..,i_min-1)
S2002
Register dissimilarity between newly generated cluster and the other clusters to a location of i_min
dist[i_min][j]←Dissimilarity between newly generated cluster and cluster corresponding to cluster_idx[j]
(j = i_min+1, ..., j_min-1, j_min+1, ..., all_clust)
S2003
Delete the element whose index is j_min from clust_idx[], and shift data following j_min forward
clust_idx[i]←clust_idx[i+1](i=j_min, ...,all_clust-1)
S2004
Delete the element whose index is j_min from dist[][], and shift data following j_min forward
dist[i][j]←dist[i+1][j](i<j and i,j = j_min, ..., all_clust)
S2005
Delete the element whose index is j_min from dist[][], and shift data following j_min forward
dist[i][j]←dist[i][j+1]
(i<j and i = 1,...,all_clust-1 and j = j_min,...,all_clust-1)
S2006
Subtract 1 from all_clust indicating total number of clusters to be joined
all_clust←all_clust-1
S2007
Set clusterNo to be assigned to new cluster structure
newclusterNo←newclusterNo+1
2

Fig. 21

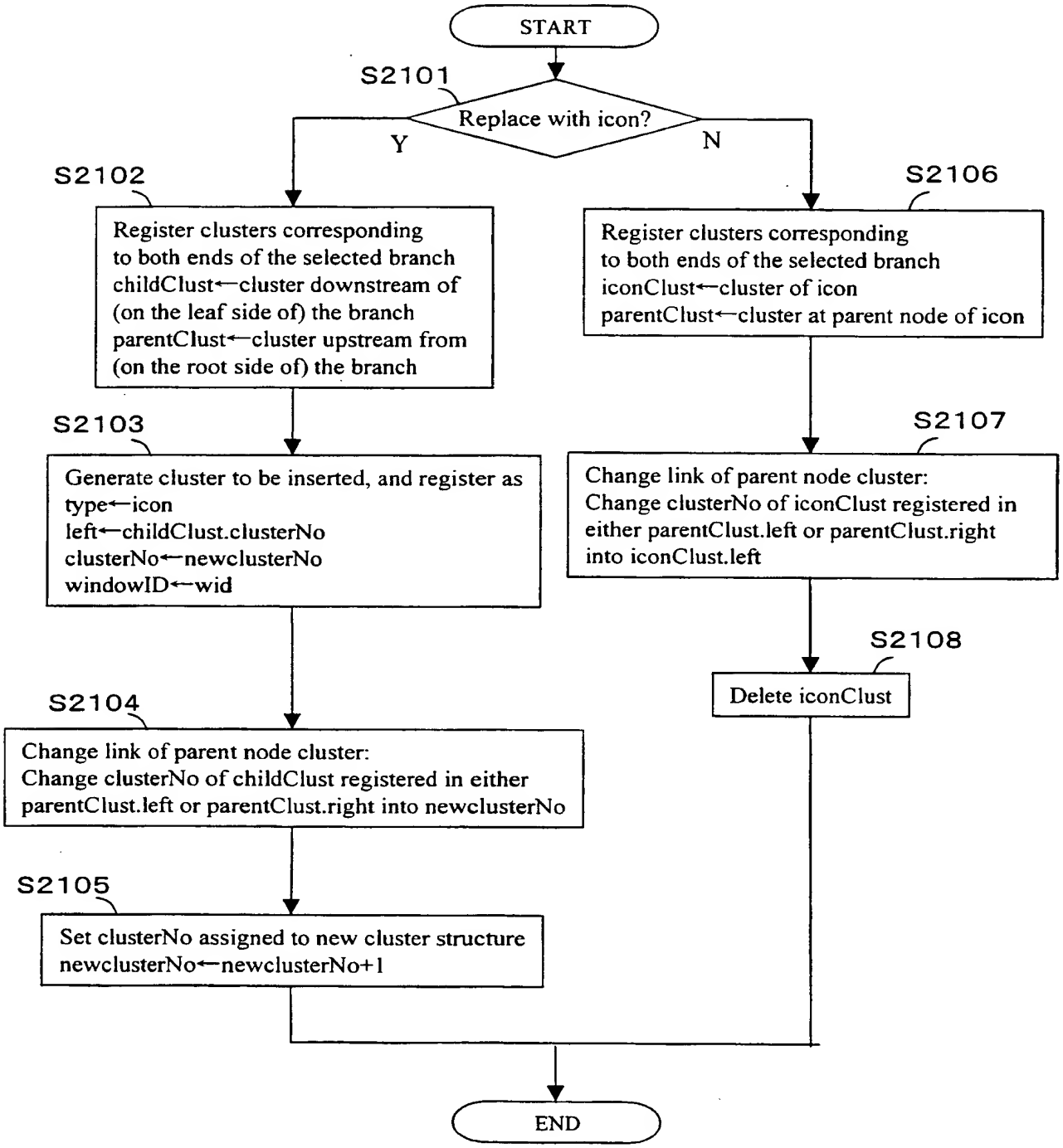

START
S2101
Replace with icon?
Y
N
S2102
Register clusters corresponding to both ends of the selected branch
childClust←cluster downstream of (on the leaf side of) the branch
parentClust←cluster upstream from (on the root side of) the branch
S2103
Generate cluster to be inserted, and register as
type←icon
left←childClust.clusterNo
clusterNo←newclusterNo
windowID←wid
S2104
Change link of parent node cluster:
Change clusterNo of childClust registered in either parentClust.left or parentClust.right into newclusterNo
S2105
Set clusterNo assigned to new cluster structure
newclusterNo←newclusterNo+1
S2106
Register clusters corresponding to both ends of the selected branch
iconClust←cluster of icon
parentClust←cluster at parent node of icon
S2107
Change link of parent node cluster:
Change clusterNo of iconClust registered in either parentClust.left or parentClust.right into iconClust.left
S2108
Delete iconClust
END

Fig. 22

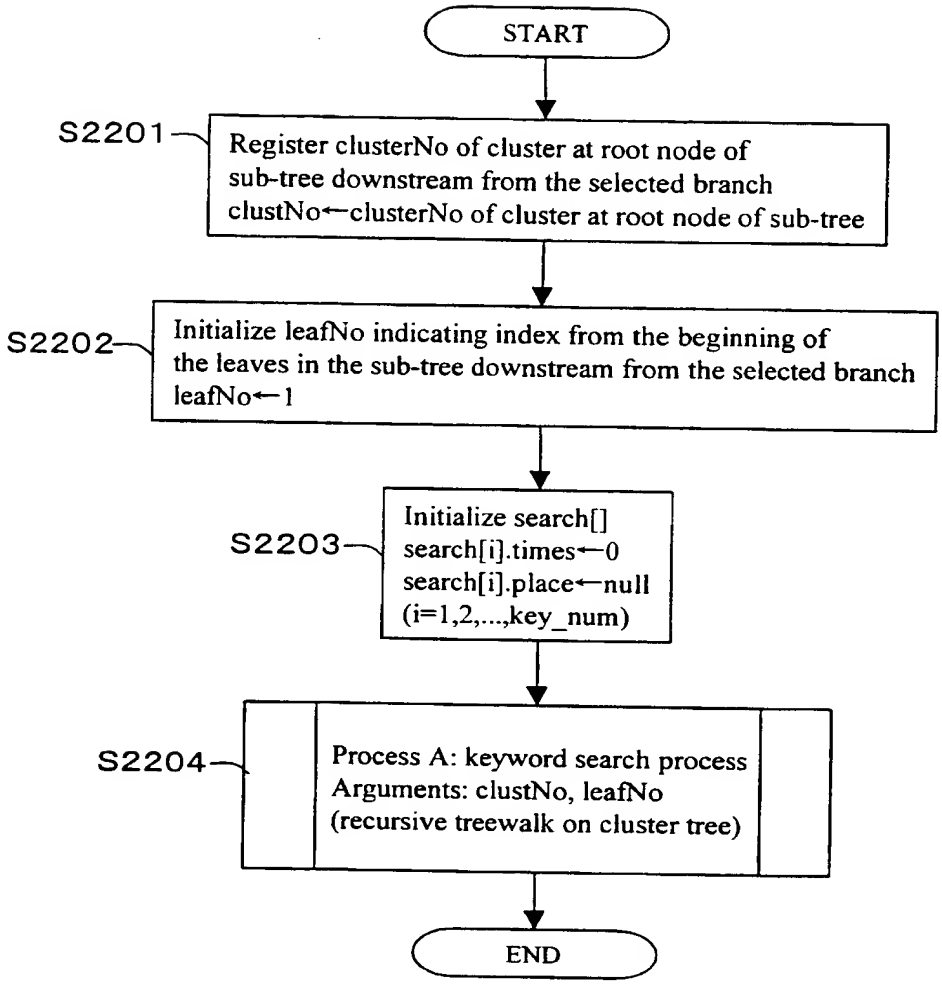

START
S2201
Register clusterNo of cluster at root node of sub-tree downstream from the selected branch
clustNo←clusterNo of cluster at root node of sub-tree
S2202
Initialize leafNo indicating index from the beginning of the leaves in the sub-tree downstream from the selected branch
leafNo←1
S2203
Initialize search[]
search[i].times←0
search[i].place←null
(i=1,2,...,key_num)
S2204
Process A: keyword search process
Arguments: clustNo, leafNo
(recursive treewalk on cluster tree)
END

Fig. 23

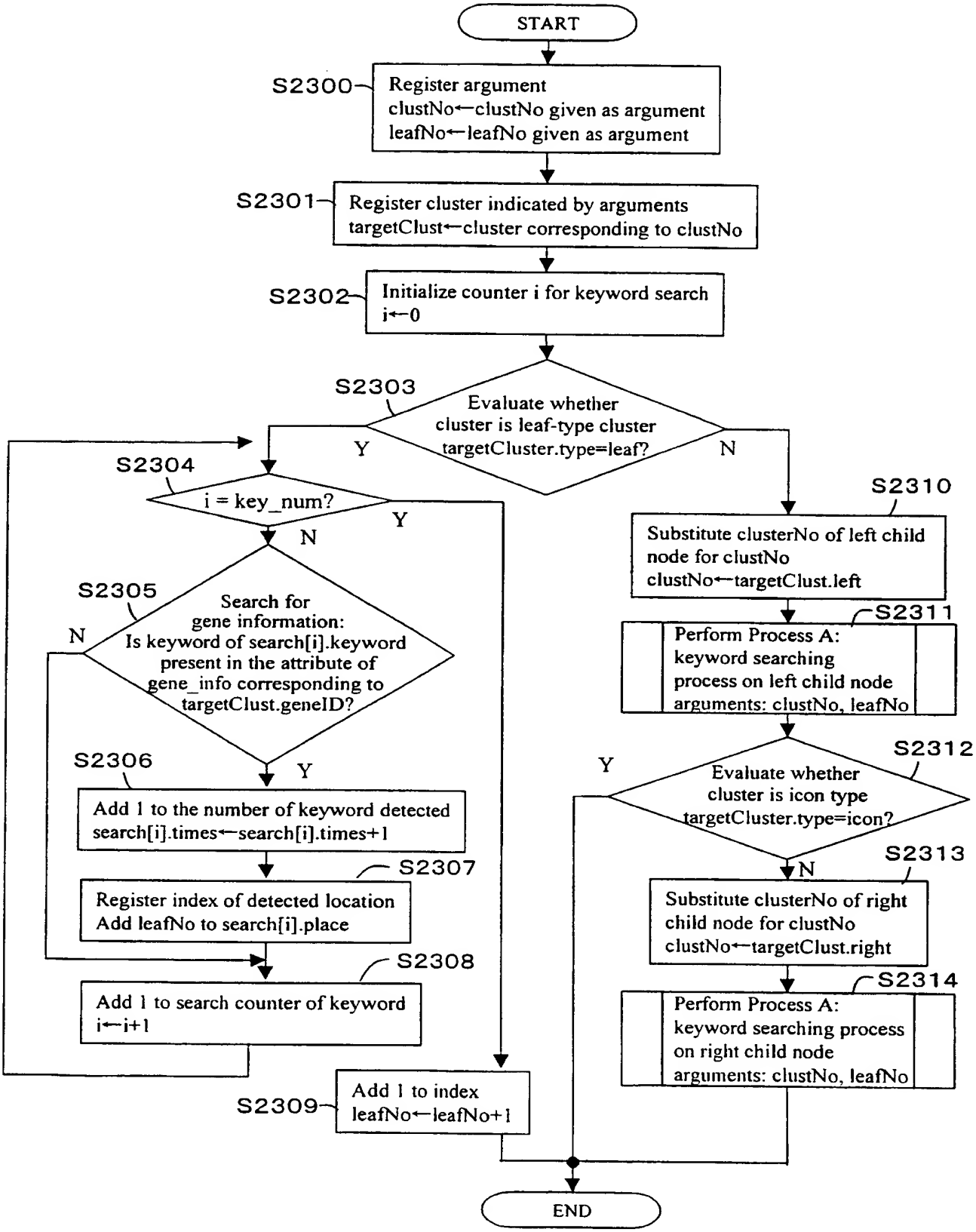

START
S2300
Register argument
clustNo←clustNo given as argument
leafNo←leafNo given as argument
S2301
Register cluster indicated by arguments
targetClust←cluster corresponding to clustNo
S2302
Initialize counter i for keyword search
i←0
S2303
Evaluate whether cluster is leaf-type cluster
targetCluster.type=leaf?
Y
N
S2304
i = key_num?
Y
N
S2305
Search for gene information:
Is keyword of search[i].keyword present in the attribute of gene_info corresponding to targetClust.geneID?
N
Y
S2306
Add 1 to the number of keyword detected
search[i].times←search[i].times+1
S2307
Register index of detected location
Add leafNo to search[i].place
S2308
Add 1 to search counter of keyword
i←i+1
S2309
Add 1 to index
leafNo←leafNo+1
S2310
Substitute clusterNo of left child node for clustNo
clustNo←targetClust.left
S2311
Perform Process A:
keyword searching process on left child node
arguments: clustNo, leafNo
S2312
Evaluate whether cluster is icon type
targetCluster.type=icon?
Y
N
S2313
Substitute clusterNo of right child node for clustNo
clustNo←targetClust.right
S2314
Perform Process A:
keyword searching process on right child node
arguments: clustNo, leafNo
END

Fig. 24

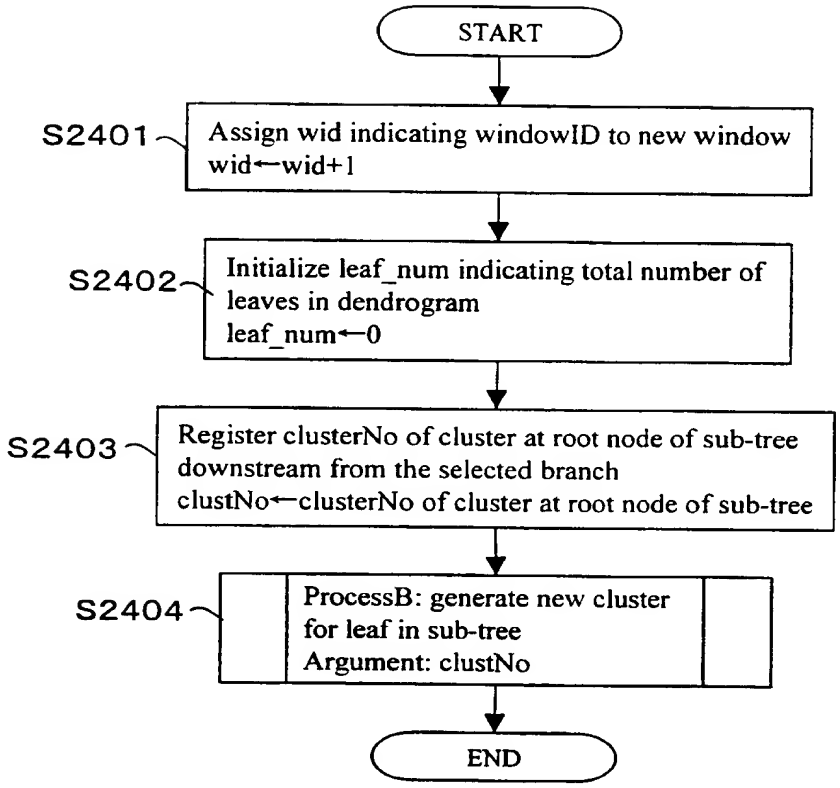
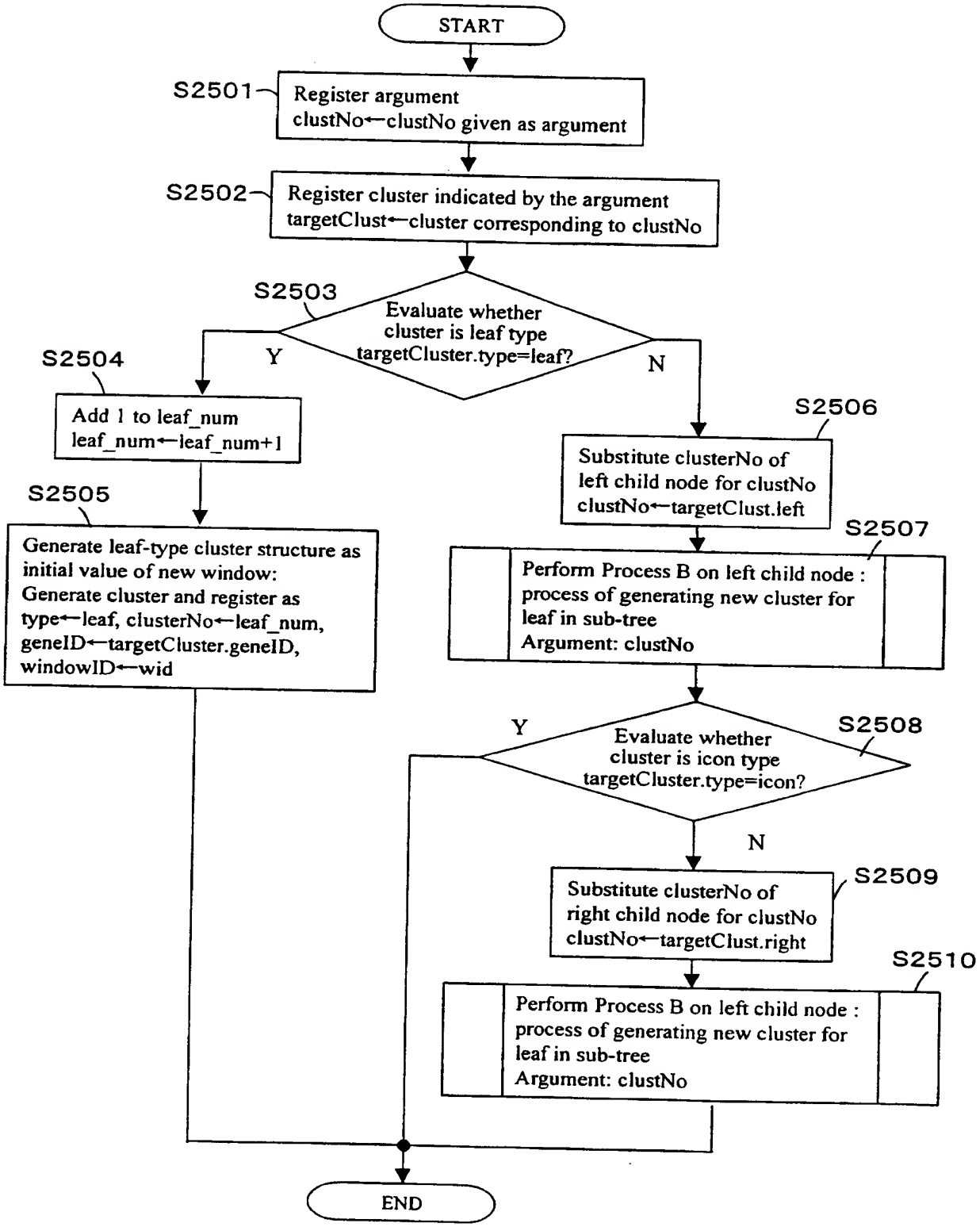

START
S2401
Assign wid indicating windowID to new window
wid←wid+1
S2402
Initialize leaf_num indicating total number of leaves in dendrogram
leaf_num←0
S2403
Register clusterNo of cluster at root node of sub-tree downstream from the selected branch
clustNo←clusterNo of cluster at root node of sub-tree
S2404
ProcessB: generate new cluster for leaf in sub-tree
Argument: clustNo
END

Fig. 25


START
S2501
Register argument
clustNo←clustNo given as argument
S2502
Register cluster indicated by the argument
targetClust←cluster corresponding to clustNo
S2503
Evaluate whether cluster is leaf type
targetCluster.type=leaf?
Y
N
S2504
Add 1 to leaf_num
leaf_num←leaf_num+1
S2505
Generate leaf-type cluster structure as initial value of new window:
Generate cluster and register as
type←leaf, clusterNo←leaf_num,
geneID←targetCluster.geneID,
windowID←wid
S2506
Substitute clusterNo of left child node for clustNo
clustNo←targetClust.left
S2507
Perform Process B on left child node : process of generating new cluster for leaf in sub-tree
Argument: clustNo
Y
S2508
Evaluate whether cluster is icon type
targetCluster.type=icon?
N
S2509
Substitute clusterNo of right child node for clustNo
clustNo←targetClust.right
S2510
Perform Process B on left child node : process of generating new cluster for leaf in sub-tree
Argument: clustNo
END